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(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number
WO 01/10380 A2(51) International Patent Classification⁷:**A61K**

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(21) International Application Number: PCT/US00/21308

(22) International Filing Date: 4 August 2000 (04.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/147,221 4 August 1999 (04.08.1999) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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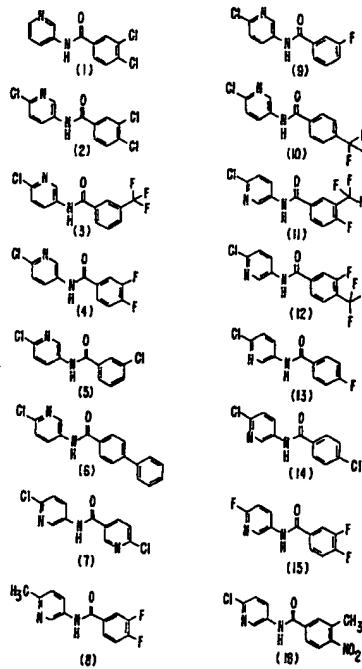
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Published:

— Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BENZANILIDES AS POTASSIUM CHANNEL OPENERS

**WO 01/10380 A2**

(57) Abstract: Benzanilides are provided which are voltage-dependent potassium channel openers. Methods of using the benzanilides of the invention are also provided.

BENZANILIDES AS POTASSIUM CHANNEL OPENERS

CROSS-REFERENCES TO RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Patent
5 Application Serial No. 60/147,221, filed on August 4, 1999, the disclosure of which is incorporated herein by reference in its entirety for all purposes.

FIELD OF THE INVENTION

This invention relates to the use of benzanilides as potassium channel
10 openers and to the treatment of diseases modulated by potassium channel opening. Additionally, this invention relates to novel compounds that are useful as potassium channel openers.

BACKGROUND OF THE INVENTION

15 Ion channels are cellular proteins that regulate the flow of ions, including calcium, potassium, sodium and chloride, into and out of cells. These channels are present in all human cells and affect such processes as nerve transmission, muscle contraction and cellular secretion. Among the ion channels, potassium channels are the most ubiquitous and diverse, being found in a variety of animal cells such as nervous,
20 muscular, glandular, immune, reproductive, and epithelial tissue. These channels allow the flow of potassium in and/or out of the cell under certain conditions. For example, the outward flow of potassium ions upon opening of these channels makes the interior of the cell more negative, counteracting depolarizing voltages applied to the cell. These channels are regulated, e.g., by calcium sensitivity, voltage-gating, second messengers,
25 extracellular ligands, and ATP-sensitivity.

Potassium channels have now been associated with a number of physiological processes, including regulation of heartbeat, dilation of arteries, release of insulin, excitability of nerve cells, and regulation of renal electrolyte transport.

Potassium channels are made by alpha subunits that fall into at least 8
30 families, based on predicted structural and functional similarities (Wei *et al.*, *Neuropharmacology* 35(7):805-829 (1997)). Three of these families (Kv, eag-related, and KQT) share a common motif of six transmembrane domains and are primarily gated by voltage. Two other families, CNG and SK/IK, also contain this motif but are gated by cyclic nucleotides and calcium, respectively. The three other families of potassium

channel alpha subunits have distinct patterns of transmembrane domains. Slo family potassium channels, or BK channels have seven transmembrane domains (Meera *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 94(25):14066-71 (1997)) and are gated by both voltage and calcium or pH (Schreiber *et al.*, *J. Biol. Chem.* 273:3509-16 (1998)). Another family, the 5 inward rectifier potassium channels (Kir), belong to a structural family containing two transmembrane domains, and an eighth functionally diverse family (TP, or “two-pore”) contains two tandem repeats of this inward rectifier motif.

Potassium channels are typically formed by four alpha subunits, and can be homomeric (made of identical alpha subunits) or heteromeric (made of two or more 10 distinct types of alpha subunits). In addition, potassium channels made from Kv, KQT and Slo or BK subunits have often been found to contain additional, structurally distinct auxiliary, or beta, subunits. These subunits do not form potassium channels themselves, but instead they act as auxiliary subunits to modify the functional properties of channels formed by alpha subunits. For example, the Kv beta subunits are cytoplasmic and are 15 known to increase the surface expression of Kv channels and/or modify inactivation kinetics of the channel (Heinemann *et al.*, *J. Physiol.* 493:625-633 (1996); Shi *et al.*, *Neuron* 16(4):843-852 (1996)). In another example, the KQT family beta subunit, minK, primarily changes activation kinetics (Sanguinetti *et al.*, *Nature* 384:80-83 (1996)).

Slo or BK potassium channels are large conductance potassium channels 20 found in a wide variety of tissues, both in the central nervous system and periphery. They play a key role in the regulation of processes such as neuronal integration, muscular contraction and hormone secretion. They may also be involved in processes such as lymphocyte differentiation and cell proliferation, spermatocyte differentiation and sperm motility. Three alpha subunits of the Slo family have been cloned, i.e., Slo1, Slo2, and 25 Slo3 (Butler *et al.*, *Science* 261:221-224 (1993); Schreiber *et al.*, *J. Biol. Chem.*, 273:3509-16 (1998); and Joiner *et al.*, *Nature Neurosci.* 1: 462-469 (1998)). These Slo family members have been shown to be voltage and/or calcium gated, and/or regulated by intracellular pH.

Certain members of the Kv family of potassium channels were recently 30 renamed (see Biervert, *et al.*, *Science* 279:403-406 (1998)). KvLQT1 was re-named KCNQ1, and the KvLQT1-related channels (KvLR1 and KvLR2) were renamed KCNQ2 and KCNQ3, respectively. More recently, a fourth member of the KCNQ subfamily was identified (KCNQ4) as a channel expressed in sensory outer hair cells (Kubisch, *et al.*, *Cell* 96(3):437-446 (1999)).

KCNQ2 and KCNQ3 have been shown to be nervous system-specific potassium channels associated with benign familial neonatal convulsions ("BFNC"), a class of idiopathic generalized epilepsy (see, Leppert, *et al.*, *Nature* 337:647-648 (1989)). These channels have been linked to M-current channels (see Wang, *et al.*, *Science* 282:1890-1893 (1998)). The discovery and characterization of these channels and currents provides useful insights into how these voltage dependent (K_v) potassium channels function in different environments, and how they respond to various activation mechanisms. Such information has now led to the identification of modulators of KCNQ2 and KCNQ3 potassium channels or the M-current, and the use of such modulators as therapeutic agents. The modulators are the subject of the present invention.

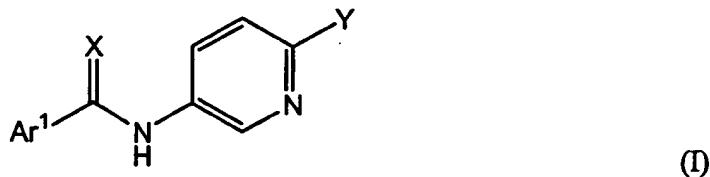
Bioactive compounds based on a benzanilide motif are known for the treatment of circulatory disturbances (Arita *et al.*, U.S. Patent No. 5,958,944), fungal infections (Baker *et al.*, U.S. Patent No. 4,845,107), inflammation (Beeley *et al.*, U.S. Patent No. 5,340,827) and ulcers and bacterial infections (Nishino *et al.*, 5,859,032). The previous benzanilides do not include the 2-substituted-5-aminopyridine substructure found in the compounds of the present invention. Moreover, none of the known benzanilide analogues are disclosed to modulate potassium channels or to be of use in treating conditions involving the modulation of potassium channels.

20

SUMMARY OF THE INVENTION

The present invention provides compounds which are useful in the treatment of diseases through the modulation of potassium ion flux through voltage-dependent potassium channels. More particularly, the invention provides compounds, compositions and methods that are useful in the treatment of central or peripheral nervous system disorders (e.g., migraine, ataxia, Parkinson's disease, bipolar disorders, trigeminal neuralgia, spasticity, mood disorders, brain tumors, psychotic disorders, myokymia, seizures, epilepsy, hearing and vision loss, Alzheimer's disease, age-related memory loss, learning deficiencies, anxiety and motor neuron diseases, and as neuroprotective agents (e.g., to prevent stroke and the like)).

In one aspect, the present invention provides compounds having a structure according to Formula I:



in which the symbol Ar¹ represents a member selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl. The letter X represents a member selected from the group consisting of O, S and N-R¹, in which R¹ is H, (C₁-C₈)alkyl,
 5 substituted (C₁-C₈)alkyl, heteroalkyl, substituted heteroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl, substituted aryl(C₁-C₄)alkyl, CN, -C(O)R², -OR³, -C(O)NR³R⁴, or -S(O)₂NR³R⁴. The symbol R² represents a member selected from the group consisting of (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, cycloalkyl,
 substituted cycloalkyl, heteroalkyl, substituted heteroalkyl, heterocyclyl, substituted
 10 heterocyclyl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl and substituted aryl(C₁-C₄)alkyl. R³ and R⁴ are each members independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, cycloalkyl,
 substituted cycloalkyl, heteroalkyl, substituted heteroalkyl, heterocyclyl, substituted
 15 heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl and substituted aryl(C₁-C₄)alkyl. Alternatively, R³ and R⁴ can be combined with the nitrogen to which each is attached to form a 5-, 6- or 7-membered ring, optionally having additional heteroatoms at the ring vertices. The letter Y represents a member selected from the group consisting of halogen, C₁-C₄ alkyl, C₁-C₄ substituted alkyl, -OCH₃ and -OCF₃.

20 In another aspect, the present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable excipient and a compound having a structure according to Formula II:



in which the symbols Ar¹ and Ar² independently represent aryl, substituted aryl,
 25 heteroaryl and substituted heteroaryl. The letter represents O, S or N-R¹, in which R¹ is a H, (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl, substituted aryl(C₁-C₄)alkyl, CN, -C(O)R², -OR³, -C(O)NR³R⁴, or -S(O)₂NR³R⁴. The symbol R² represents (C₁-C₈)alkyl, substituted (C₁-

C_8)alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C_1 - C_4)alkyl or substituted aryl(C_1 - C_4)alkyl. R^3 and R^4 are each members independently selected from the group consisting of hydrogen, (C_1 - C_8)alkyl, substituted (C_1 - C_8)alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C_1 - C_4)alkyl and substituted aryl(C_1 - C_4)alkyl.

5 Alternatively, R^3 and R^4 can be combined with the nitrogen to which each is attached to form a 5-, 6- or 7-membered ring optionally having additional heteroatoms at the ring vertices.

In yet another aspect, the present invention provides a method for modulating ion flux through voltage dependent potassium channels, comprising 10 contacting a cell containing the target ion channels with a compound according to Formula II, above.

In still another aspect, the present invention provides a method for the treatment of diseases through modulation of ion flux through voltage dependent potassium channels, the method comprising treating the host with an effective amount of 15 a potassium channel compound of Formula II, above.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a tabulation of 100 representative compounds of the invention.

20 **DETAILED DESCRIPTION OF THE INVENTION AND
THE PREFERRED EMBODIMENTS**

Abbreviations and Definitions:

The abbreviations used herein have their conventional meaning within the 25 chemical and biological arts. For example: CHO, Chinese hamster ovary; EBSS, Earl's Balanced Salt Solution; KCNQ, potassium channel Q; KCNQ2, potassium channel Q2; SDS, sodium dodecyl sulfate; Et₃N: triethylamine; MeOH: methanol; and DMSO: dimethylsulfoxide.

The term "alkyl," by itself or as part of another substituent, means, unless 30 otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* C_1 - C_{10} means one to ten carbons). Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl,

cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 5 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "alkyl," unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below as "heteroalkyl." Alkyl groups which are limited to hydrocarbon groups are termed "homoalkyl".

The term "alkylene" by itself or as part of another substituent means a 10 divalent radical derived from an alkane, as exemplified by -CH₂CH₂CH₂CH₂-, and further includes those groups described below as "heteroalkylene." Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer 15 carbon atoms.

The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

The term "heteroalkyl," by itself or in combination with another term, 20 means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed 25 at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, and -CH=CH-N(CH₃)-CH₃. Up to two heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ 30 and -CH₂-O-Si(CH₃)₃. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by -CH₂-CH₂-S-CH₂CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂- For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy,

alkylenedioxy, alkyleneamino, alkylidendiamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of 5 "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1 10 -(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and 15 polyhaloalkyl. For example, the term "halo(C₁-C₄)alkyl" is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term "heteroaryl" 20 refers to aryl groups (or rings) that contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl

group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxyethyl, 2-pyridyloxymethyl, 3-(1-naphthoxy)propyl, and the like).

5 Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl" and "heteroaryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, 10 heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups selected from, for example: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R'R'', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR'R'', -NR''C(O)₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -CN and -NO₂ in a number ranging from 15 zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R'' and R''' each independently refer to hydrogen, unsubstituted (C₁-C₈)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C₁-C₄)alkyl groups. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. Thus, -NR'R'' is meant to include, for example, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as haloalkyl (*e.g.*, -CF₃ and -CH₂CF₃) and acyl (*e.g.*, -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

Similarly, substituents for the aryl and heteroaryl groups are varied and are 25 selected from, for example: -halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -C(O)R', -OC(O)NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NR'-C(O)NR'R'', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -N₃, -CH(Ph)₂, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the 30 aromatic ring system; and where R', R'' and R''' are independently selected from, for example, hydrogen, (C₁-C₈)alkyl and heteroalkyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-(C₁-C₄)alkyl, and (unsubstituted aryl)oxy-(C₁-C₄)alkyl.

Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH₂)_q-U-, wherein

T and U are independently -NH-, -O-, -CH₂- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CH₂)_s-X-(CH₂)_t-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-.

5 The substituent R' in -NR'- and -S(O)₂NR'- is selected from hydrogen or unsubstituted (C₁-C₆)alkyl.

10

As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of 15 pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically 20 acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, 25 succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Certain specific compounds of the present 30

invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner.

5 The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which

are in a prodrug form. Prodrugs of the compounds described herein are those compounds

10 that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or
15 chemical reagent.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple

20 crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers
25 and individual isomers are all intended to be encompassed within the scope of the present invention.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes,
30 such as for example tritium (³H), iodine-125 (¹²⁵I) or carbon-14 (¹⁴C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

Introduction

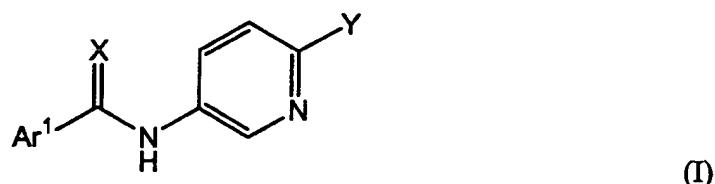
The development of therapeutic agents, which act on potassium ion channels, has received considerable recent attention. One group has described a family of N-alkyl benzamides that act by blocking I_{K_s} potassium channels (see PCT/US98/02364, 5 published as WO 98/37068). Surprisingly, the N-aryl benzamides and related compounds provided herein, act by *opening* the KCNQ potassium channels.

In view of the above-noted discovery, the present invention provides compounds, compositions, and methods for increasing ion flux in voltage-dependent potassium channels, particularly those channels responsible for the M-current. As used 10 herein, the term "M-current," "channels responsible for the M-current" and the like, refers to a slowly activating, non-inactivating, slowly deactivating voltage-gated K^+ channel. M-current is active at voltages close to the threshold for action potential generation in a wide variety of neuronal cells, and thus, is an important regulator of neuronal excitability.

Recently, members of the voltage-dependent potassium channel family 15 have been shown to be directly involved in diseases of the central or peripheral nervous system. The benzamides provided herein are now shown to act as KCNQ channel openers, particularly for KCNQ2 and KCNQ3, as well as the heteromultimer channels such as KCNQ2/3 or the M-current.

20 Description of the Embodiments**I. MODULATORS OF VOLTAGE-DEPENDENT POTASSIUM CHANNELS**

In view of the above surprising discovery, the present invention provides in one aspect, compounds according to Formula I:



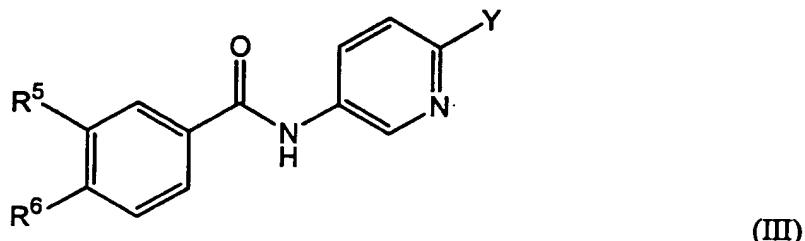
25 in which the symbol Ar^1 represents a member selected from the group consisting of aryl, substituted aryl, heteroaryl and substituted heteroaryl. The letter X represents a member selected from the group consisting of O, S and $N-R^1$, in which R^1 is H, (C_1-C_8) alkyl, substituted (C_1-C_8) alkyl, heteroalkyl, substituted heteroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl (C_1-C_4) alkyl, substituted aryl (C_1-C_4) alkyl, CN, - $C(O)R^2$, - OR^3 , - $C(O)NR^3R^4$, or - $S(O)_2NR^3R^4$. The symbol R^2 represents a member 30 selected from the group consisting of (C_1-C_8) alkyl, substituted (C_1-C_8) alkyl, cycloalkyl,

substituted cycloalkyl, heteroalkyl, substituted heteroalkyl, heterocyclyl, substituted heterocyclyl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl and substituted aryl(C₁-C₄)alkyl. R³ and R⁴ are each members independently selected from the group consisting of hydrogen, (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, cycloalkyl, 5 substituted cycloalkyl, heteroalkyl, substituted heteroalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl and substituted aryl(C₁-C₄)alkyl. Alternatively, R³ and R⁴ can be combined with the nitrogen to which each is attached to form a 5-, 6- or 7-membered ring, optionally having additional heteroatoms at the ring vertices. The letter Y represents a member selected 10 from the group consisting of halogen, C₁-C₄ alkyl, C₁-C₄ substituted alkyl, -OCH₃ and -OCF₃.

In one group of preferred embodiments, Ar¹ phenyl, substituted phenyl, indolyl, substituted indolyl, benzofuranyl, substituted benzofuranyl, furanyl, substituted furanyl, thienyl, substituted thienyl, isothiazolyl, substituted isothiazolyl, pyrazolyl or 15 substituted pyrazolyl. Still further preferred are those embodiments in which Ar¹ is substituted phenyl, substituted or unsubstituted 2-indolyl and substituted or unsubstituted 2-thienyl. In yet another group of preferred embodiments, X is O.

In those preferred embodiments, in which Ar¹ is substituted, the Ar¹ substituents are halogen, alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, 20 nitro, cyano, -N R⁷C(O) R⁸, -N R⁷R⁸, phenyl and/or substituted phenyl. The symbols R⁷ and R⁸ independently represent hydrogen, (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, cycloalkyl, substituted cycloalkyl, heteroalkyl, substituted heteroalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl and substituted aryl(C₁-C₄)alkyl. Alternatively, R⁷ and R⁸ are combined with 25 the nitrogen to which it is attached to form a 5-, 6- or 7-membered ring, optionally having additional heteroatoms at the ring vertices.

In yet a further group of preferred embodiments, the compounds of the invention have a structure according to Formula III:



in which the symbols R⁵ and R⁶ independently represent H, halogen, alkyl, halo(C₁-C₄)alkyl, nitro, cyano or phenyl, with the proviso that both R⁵ and R⁶ are not H. In a still further group of preferred embodiments, the symbols R⁵ and R⁶ independently represent H, F, and Cl.

5 Certain combinations of the above preferred embodiments form a group of particularly preferred compounds. Accordingly, one certain preferred compounds of the present invention are those set forth in FIG. 1, appended hereto.

10 Also within the scope of the present invention are compounds of the invention that function as poly- or multi-valent species, including, for example, species such as dimers, trimers, tetramers and higher homologs of the compounds of the invention or reactive analogues thereof. The poly- and multi-valent species can be assembled from a single species or more than one species of the invention. For example, a dimeric construct can be "homo-dimeric" or "heterodimeric." Moreover, poly- and multi-valent constructs in which a compound of the invention or reactive analogues thereof are attached to an oligomeric or polymeric framework (e.g., polylysine, dextran, hydroxyethyl starch and the like) are within the scope of the present invention. The framework is preferably polyfunctional (*i.e.* having an array of reactive sites for attaching compounds of the invention). Moreover, the framework can be derivatized with a single species of the invention or more than one species of the invention.

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Preparation of Potassium Channel Openers

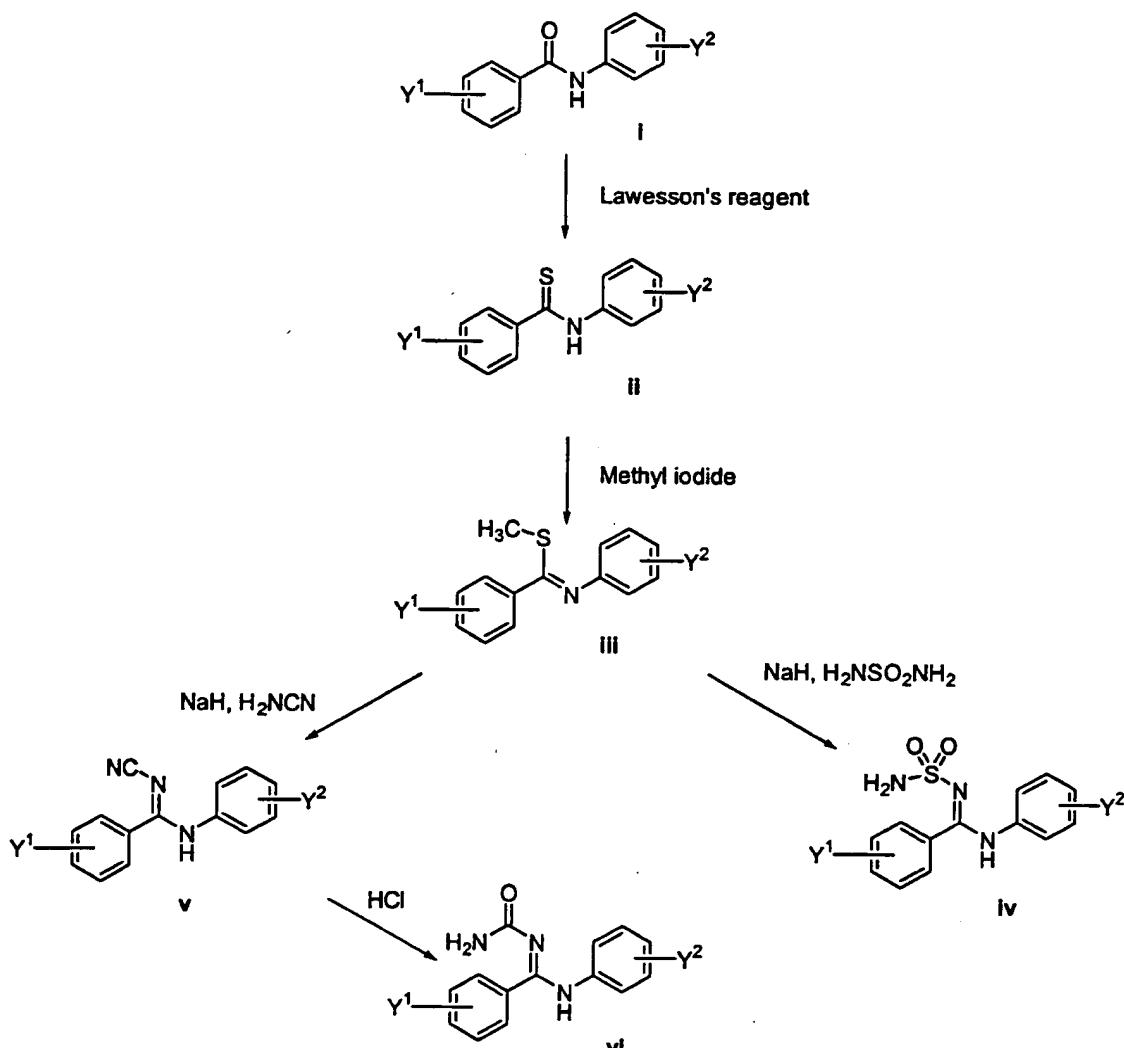
Compounds of the present invention can be prepared using readily available starting materials or known intermediates. Briefly, the synthesis of N-aryl benzamides involves formation of a single amide bond from a "carbonyl component" (typically a carboxylic acid, carboxylic acid chloride, ester or an activated form of a carboxylic acid, for example, a symmetrical or mixed anhydride) and an "amine component" (typically, an aniline, aniline derivative, amino heterocycle, and the like). General and specific procedures for the preparation of the present compounds are provided in the examples below.

30 Other compounds of the present invention can be prepared using standard procedures as outlined in Scheme 1 below. In this scheme, an N-phenyl benzamide (i, wherein Y¹ and Y² represent substituents, including multiple substituents on the aryl groups) can be treated with reagents such as Lawesson's reagent to provide the thioamides, ii. Alkylation of ii, with, for example, methyl iodide produces iii which can

be converted to target structures **iv**, **v** and **vi**. Thus, treatment of **iii** with sodium hydride (or another suitable base) and sulfamide provides the sulfamoylimino derivative, **iv**. Similarly, treatment of **iii** with sodium hydride or another base, followed by cyanamide provides **v**. Conversion of **v** to **vi** can be accomplished with HCl.

One of skill in the art will recognize that other compounds of the present invention can be prepared from intermediates such as **iii**. For example, treatment of **iii** with a primary or secondary amine will provide amidine derivatives that are useful as described or they can be further derivatized.

SCHEME 1



10

Methods for preparing dimers, trimers and higher homologs of small organic molecules, such as those of the present invention, as well as methods of

functionalizing a polyfunctional framework molecule are well known to those of skill in the art. For example, an aromatic amine of the invention is converted to the corresponding isothiocyanate by the action of thiophosgene. The resulting isothiocyanate is coupled to an amine of the invention, thereby forming either a homo- or heterodimeric species. Alternatively, the isothiocyanate is coupled with an amine-containing backbone, such as polylysine, thereby forming a conjugate between a polyvalent framework and a compound of the invention. If it is desired to prepare a heterofunctionalized polyvalent species, the polylysine is underlabeled with the first isothiocyanate and subsequently labeled with one or more different isothiocyanates. Alternatively, a mixture of isothiocyanates is added to the backbone. Purification proceeds by, for example, size exclusion chromatography, dialysis, nanofiltration and the like.

II. ASSAYS FOR MODULATORS OF KCNQ CHANNELS

KCNQ monomers as well as KCNQ alleles and polymorphic variants are subunits of potassium channels. The activity of a potassium channel comprising KCNQ subunits can be assessed using a variety of *in vitro* and *in vivo* assays, e.g., measuring current, measuring membrane potential, measuring ion flux, e.g., potassium or rubidium, measuring potassium concentration, measuring second messengers and transcription levels, using potassium-dependent yeast growth assays, and using e.g., voltage-sensitive dyes, radioactive tracers, and patch-clamp electrophysiology.

Furthermore, such assays can be used to test for inhibitors and activators of channels comprising KCNQ. Such modulators of a potassium channel are useful for treating various disorders involving potassium channels, including but not limited to, for example, central and peripheral nervous system disorders (e.g., migraine, ataxia, Parkinson's disease, bipolar disorders, spasticity, mood disorders, brain tumors, psychotic disorders, myokymia, seizures, epilepsy, hearing and vision loss, Alzheimer's disease, age-related memory loss, learning deficiencies, and motor neuron diseases, and can also be used as neuroprotective agents (e.g., to prevent stroke and the like). Such modulators are also useful for investigation of the channel diversity provided by KCNQ and the regulation/modulation of potassium channel activity provided by KCNQ.

Modulators of the potassium channels are tested using biologically active KCNQ, either recombinant or naturally occurring, or by using native cells, like cells from the nervous system expressing the M-current. KCNQ can be isolated, co-expressed or expressed in a cell, or expressed in a membrane derived from a cell. In such assays,

KCNQ2 is expressed alone to form a homomeric potassium channel or is co-expressed with a second subunit (e.g., another KCNQ family member, preferably KCNQ3) so as to form a heteromeric potassium channel. Modulation is tested using one of the *in vitro* or *in vivo* assays described above. Samples or assays that are treated with a potential

5 potassium channel inhibitor or activator are compared to control samples without the test compound, to examine the extent of modulation. Control samples (untreated with activators or inhibitors) are assigned a relative potassium channel activity value of 100. Activation of channels comprising KCNQ2 is achieved when the potassium channel activity value relative to the control is 110%, more preferably 130%, more preferably 10 170% higher. Compounds that increase the flux of ions will cause a detectable increase in the ion current density by increasing the probability of a channel comprising KCNQ2 being open, by decreasing the probability of it being closed, by increasing conductance through the channel, and increasing the number or expression of channels.

Changes in ion flux may be assessed by determining changes in polarization (i.e., electrical potential) of the cell or membrane expressing the potassium channel comprising KCNQ2, KCNQ2/3 or the M-current. A preferred means to determine changes in cellular polarization is by measuring changes in current or voltage with the voltage-clamp and patch-clamp techniques, using the "cell-attached" mode, the "inside-out" mode, the "outside-out" mode, the "perforated cell" mode, the "one or two electrode" mode, or the "whole cell" mode (see, e.g., Ackerman *et al.*, *New Engl. J. Med.* 336:1575-1595 (1997)). Whole cell currents are conveniently determined using the standard methodology (see, e.g., Hamil *et al.*, *Pflugers. Archiv.* 391:85 (1981). Other known assays include: radiolabeled rubidium flux assays and fluorescence assays using voltage-sensitive dyes (see, e.g., Vestergaard-Bogind *et al.*, *J. Membrane Biol.* 88:67-75 20 (1988); Daniel *et al.*, *J. Pharmacol. Meth.* 25:185-193 (1991); Holevinsky *et al.*, *J. Membrane Biology* 137:59-70 (1994)). Assays for compounds capable of inhibiting or increasing potassium flux through the channel proteins comprising KCNQ2 or heteromultimers of KCNQ subunits can be performed by application of the compounds to a bath solution in contact with and comprising cells having a channel of the present invention (see, e.g., Blatz *et al.*, *Nature* 323:718-720 (1986); Park, *J. Physiol.* 481:555-30 570 (1994)). Generally, the compounds to be tested are present in the range from 1 pM to 100 mM.

The effects of the test compounds upon the function of the channels can be measured by changes in the electrical currents or ionic flux or by the consequences of

changes in currents and flux. Changes in electrical current or ionic flux are measured by either increases or decreases in flux of ions such as potassium or rubidium ions. The cations can be measured in a variety of standard ways. They can be measured directly by concentration changes of the ions or indirectly by membrane potential or by radio-

5 labeling of the ions. Consequences of the test compound on ion flux can be quite varied. Accordingly, any suitable physiological change can be used to assess the influence of a test compound on the channels of this invention. The effects of a test compound can be measured by a toxin binding assay. When the functional consequences are determined using intact cells or animals, one can also measure a variety of effects such as transmitter 10 release (e.g., dopamine), hormone release (e.g., insulin), transcriptional changes to both known and uncharacterized genetic markers (e.g., northern blots), cell volume changes (e.g., in red blood cells), immunoresponses (e.g., T cell activation), changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as Ca^{2+} , or cyclic nucleotides.

15 Preferably, the KCNQ2 that is a part of the potassium channel used in the assay will have the sequence provided in PCT/US98/13276 or a conservatively modified variant thereof. Alternatively, the KCNQ2 of the assay will be derived from a eukaryote.

KCNQ2 orthologs will generally confer substantially similar properties on a channel comprising such KCNQ2, as described above. In a preferred embodiment, the 20 cell placed in contact with a compound that is suspected to be a KCNQ2 homolog is assayed for increasing or decreasing ion flux in a eukaryotic cell, e.g., an oocyte of *Xenopus* (e.g., *Xenopus laevis*) or a mammalian cell such as a CHO or HeLa cell. Channels that are affected by compounds in ways similar to KCNQ2 are considered homologs or orthologs of KCNQ2.

25

III. PHARMACEUTICAL COMPOSITIONS OF POTASSIUM CHANNEL OPENERS

In another aspect, the present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable excipient and a compound 30 according to Formula II, above.

Formulation of the Compounds (Compositions)

The compounds of the present invention can be prepared and administered in a wide variety of oral, parenteral and topical dosage forms. Thus, the compounds of

the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered 5 transdermally. Accordingly, the present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient and either a compound of formula (I) or a pharmaceutically acceptable salt of a compound of formula (I).

For preparing pharmaceutical compositions from the compounds of the 10 present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substance, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

15 In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from 5% or 10% to 70% of the 20 active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component 25 with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed 30 homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as 5 natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may 10 contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package 15 containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 10000 mg, more typically 1.0 mg to 1000 mg, most typically 20 10 mg to 500 mg, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

IV. METHODS FOR INCREASING ION FLOW IN VOLTAGE-DEPENDENT 25 POTASSIUM CHANNELS

In yet another aspect, the present invention provides methods for increasing ion flow through voltage dependent potassium channels in a cell, comprising contacting a cell containing the target ion channels with a compound of Formula II, above.

The methods provided in this aspect of the invention are useful for the diagnosis of conditions that can be treated by modulating ion flux through voltage-dependent potassium channels, or for determining if a patient will be responsive to therapeutic agents which act by opening potassium channels. In particular, a patient's cell sample can be obtained and contacted with a compound of Formula II and the ion

flux can be measured relative to a cell's ion flux in the absence of a compound of Formula II. An increase in ion flux will typically indicate that the patient will be responsive to a therapeutic regimen of ion channel openers.

5 **V. METHODS FOR TREATING CONDITIONS MEDIATED BY VOLTAGE-DEPENDENT POTASSIUM CHANNELS**

In still another aspect, the present invention provides a method for the treatment of diseases or conditions mediated, at least in part, by voltage-dependent potassium channels. In this method, a subject suffering from such a condition or disease 10 is administered an effective amount of a compound of Formula II.

The compounds provided herein are useful as potassium channel openers and find therapeutic utility via modulation of voltage-dependent potassium channels in the treatment of diseases or conditions. The potassium channels that are typically opened are described herein as voltage-dependent potassium channels such as the KCNQ 15 potassium channels. As noted above, these channels may include homomultimers and heteromultimers of KCNQ2, KCNQ3, and KCNQ4. A heteromultimer of two proteins, e.g., KCNQ2 and KCNQ3 is referred to as, for example, KCNQ2/3. The conditions that can be treated with the compounds and compositions of the present invention may include, but are not limited to, central or peripheral nervous system disorders (e.g., 20 migraine, ataxia, Parkinson's disease, bipolar disorders, spasticity, mood disorders, brain tumors, psychotic disorders, myokymia, seizures, epilepsy, hearing and vision loss, Alzheimer's disease, age-related memory loss, learning deficiencies, and motor neuron diseases, and as neuroprotective agents (e.g., to prevent stroke and the like)).

In therapeutic use for the treatment of epilepsy or other neurological 25 conditions, the compounds utilized in the pharmaceutical method of the invention are administered at the initial dosage of about 0.001 mg/kg to about 1000 mg/kg daily. A daily dose range of about 0.1 mg/kg to about 100 mg/kg is more typical. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the 30 proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The materials, methods and devices of the present invention are further illustrated by the examples, which follow. These examples are offered to illustrate, but not to limit the claimed invention.

5

EXAMPLES

Example 1 sets forth representative methods of preparing 2-substituted -5-aminopyridines of use in preparing the compounds of the invention. The representative methods include the reduction of nitropyridines, rearrangement of nicotinic acids, and the displacement reactions of 2-halopyridines.

10

Examples 2 and 3 set forth a representative methods of preparing the benzanilides of the invention. Example 2 provides a method of preparing a benzanilide from an acid chloride. Example 3 provides a method of preparing a benzanilide from a carboxylic acid by generating the acid chloride *in situ*.

15

Example 4, 5, 6, and 7 set forth methods of elaborating the benzanilide nucleus. Example 4 provides a method of preparing 4-amino substituted benzanilides via a nucleophilic displacement. Example 5 provides a method for reducing an aromatic nitro group to the corresponding amine. Example 6 provides a method for preparing hydroxyl amine compounds. Example 7 provides a method for preparing sulfonamides.

20

Examples 8 and 9 set forth the characterization of a number of representative compounds of the invention. Example 8 sets forth the results of the physical characterization of the compounds. Example 9 sets forth the evaluation of the activity towards KCNQ2 of selected compounds of the invention.

General

25

In the examples below, unless otherwise stated, temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature (typically a range of from about 18-25°C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (typically, 4.5-30 mmHg) with a bath temperature of up to 60°C; the course of reactions was typically followed by TLC and reaction times are provided for illustration only; melting points are uncorrected; products exhibited satisfactory ¹H-NMR and/or microanalytical data; yields are provided for illustration only; and the following conventional abbreviations are also used: mp (melting point), L (liter(s)), mL (milliliters), mmol (millimoles), g (grams), mg (milligrams), min (minutes), and h (hours).

General Experimental.

Unless otherwise specified, all solvents (HPLC grade) and reagents were purchased from suppliers and used without further purification. Reactions were conducted under a blanket of argon unless otherwise stated. Analytical thin layer chromatography (tlc) was performed on Whatman Inc. 60 silica gel plates (0.25 mm thickness). Compounds were visualized under UV lamp (254 nm) or by developing with KMnO₄/KOH, ninhydrin or Hanessian's solution. Flash chromatography was done using silica gel from Selcetro Scientific (particle size 32-63). ¹H NMR, ¹⁹F NMR and ¹³C NMR spectra were recorded on a Varian 300 machine at 300 MHz, 282 MHz and 75.7 MHz, respectively. Melting points were recorded on a Electrothermal IA9100 apparatus and were uncorrected.

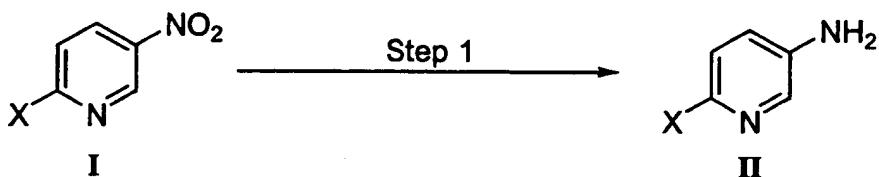
EXAMPLE 1

15 Preparation of 2-substituted-5-aminopyridines

1.1 Reduction of nitropyridines

Referring to Scheme 2, the desired aminopyridines (II) are prepared by reducing the corresponding nitropyridines (I). One skilled in the art will recognize that there are several methods to accomplish step 1. Tin chloride in DMF, hydrogenation using catalytic palladium and sodium borohydride in the presence of catalytic nickel chloride are known methods.

Scheme 2



25 1.1a Synthesis of 5-amino-2-bromopyridine

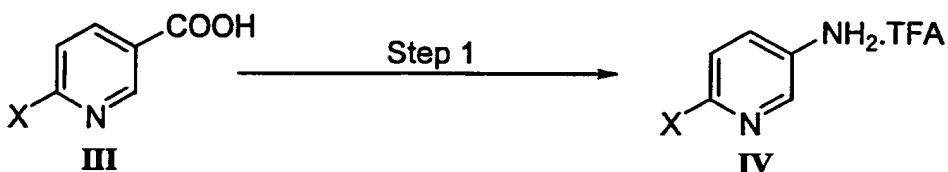
Tin (II) chloride hydrate (0.78 g, 3.5 mmol) was added to a stirring solution of 5-nitro-2-bromopyridine (0.24 g, 1.2 mmol) in DMF (5 mL) at RT. After 2 h, 6N NaOH (2 mL) was added and the suspension was stirred vigorously for 10 min. The organics were extracted with diethyl ether (2 x 10 mL), washed with brine (2 x 10 mL) and dried (Na₂SO₄). The filtered solution was then concentrated under reduced pressure

to afford the desired product as a yellow oil (0.178g, 86%), which was used without further purification.

1.2 Rearrangement of nicotinic acids

5 Rearrangement of the corresponding nicotinic acids (III) (Scheme 3) using a modified Schmidt reaction, followed by deprotection of the aniline group generated the desired aminopyridines (IV) as the corresponding TFA salts.

Scheme 3



10

1.2 a Synthesis of 5-amino-2-methylpyridine (TFA salt)

A solution of diphenylphosphorylazide (430 μ L, 2 mmol), triethylamine (278 μ L, 2 mmol) and 6-methyl-nicotinic acid (274 mg, 2 mmol) in t-butanol (30 mL) was heated at reflux for 4h. The solution was cooled to RT and poured into water (50 mL). The organics were extracted with ether (3 x 20 mL), washed with brine (2 x 10 mL) and dried (Na_2SO_4). Column chromatography (1:1 hexane/ethyl acetate) of the boc-protected aminopyridine gave the intermediate as a white solid (156 mg, 38%).

15 The desired 5-amino-2-methylpyridine-TFA salt was generated *in situ* by stirring in a 20% TFA/DCM solution (2 mL) for 4h. The solution was concentrated under reduced pressure to afford a semi-solid, which was used without further purification.

1.2 b Synthesis of 5-amino-2-(trifluoromethyl)pyridine (TFA salt)

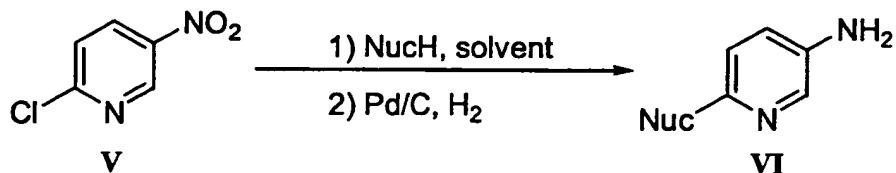
A solution of diphenylphosphorylazide (644 μ L, 3 mmol), triethylamine (417 μ L, 3 mmol) and 6-(trifluoromethyl)-nicotinic acid (573 mg, 3 mmol) in t-butanol (50 mL) was heated at reflux for 4h, then cooled to RT and poured into water (50 mL). The organics were extracted with ether (3 x 20 mL), washed with brine (2 x 10 mL) and dried (Na_2SO_4). Column chromatography (1:1 hexane/ethyl acetate) of the boc-protected aniline gave the intermediate as a white solid (389 mg, 50%).

The desired 5-amino-2-methylpyridine-TFA salt was generated *in situ* by stirring in a 20% TFA/DCM solution (2 mL) for 4h. The solution was concentrated under reduced pressure to afford a semi-solid, which was used without further purification.

1.3: Displacement of 2-halopyridines.

Several aminopyridines, which are not readily accessible via the methods outlined in schemes 1 or 2, may be synthesized via nucleophilic displacement of 2-chloropyridines as depicted in Scheme 4.

Scheme 4



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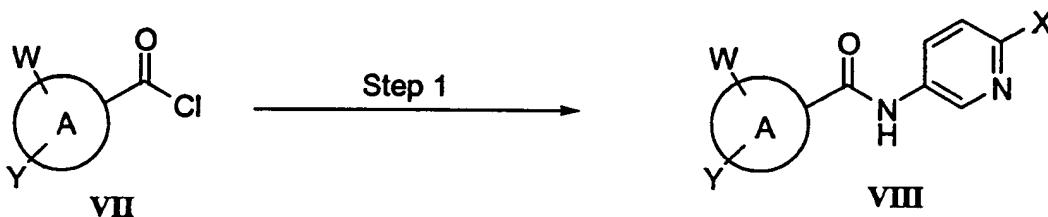
1.3a Synthesis of 5-amino-2-fluoropyridine

A mixture of 5-nitro-2-chloropyridine (2.0 g, 12.6 mmol) and anhydrous potassium fluoride (2.2 g, 38 mmol) in a combination of sulfolane (6 mL) and benzene (4 mL) was stirred at RT for 20 min. The benzene was then removed by distillation. The resulting mixture was heated at 150 °C for 12h. The mixture was cooled to RT whereupon water (60 mL) was added. The desired product was separated from the solution via steam distillation. Extraction of the distillate with diethyl ether (2 x 10 mL) followed by drying (Na_2SO_4) and concentration gave 5-nitro-2-fluoropyridine as a water white oil (1.3 g, 73%).

20 10% Palladium on charcoal (20 mg, cat) was added to a stirring solution of
5-nitro-2-fluoropyridine (100 mg, 0.7 mmol) in dichloromethane (3 mL) at RT. 1
atmosphere of hydrogen gas was then applied to the solution and the mixture was stirred
at RT for 1h. The mixture was passed through a short plug of celite and the resulting
solution, containing the desired 5-amino-2-fluoropyridine, was used without further
25 purification.

EXAMPLE 2**Preparation of Benzanilides from Acid Chlorides**

Benzanilides (*e.g.*, VIII) were prepared by reacting acid chlorides (*e.g.*, VII) with aminopyridines (*e.g.*, II, IV and VI) as shown in Scheme 5. The reaction was 5 typically conducted in the presence of a tertiary amine base such as triethylamine in an organic solvent such as dichloromethane or tetrahydrofuran, and at room temperature.

Scheme 5

A = aryl or heteroaryl

10 **2.1 General experimental for Scheme 5**

A solution of acid chloride (VII) (1 mmol) in a dry solvent (*e.g.*, acetonitrile, THF, DCM) (3 mL) was added dropwise to a stirring solution of aminopyridine (II or VI) (1 mmol) and N, N-diisopropylethylamine (1.2 mmol) in a dry solvent (*e.g.*, acetonitrile, THF, DCM) (5 mL) at RT. The resulting solution was stirred 15 for an additional 1h. If TLC analysis indicated presence of starting aniline the solution was heated at 55 °C for another 1h. After cooling to room temperature ethyl acetate (10 mL) was added and the solution was washed with water (2 x 10 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure and the crude material was purified by column chromatography (hexanes/ethyl acetate) or by crystallization 20 (hexane/dichloromethane). The products were typically white solids (50-98%). Compounds prepared via this procedure include, 1-15, 25, 27, 29 and 42.

2.1a Preparation of N-[2-chloro-5-pyridyl]-3-(trifluoromethyl)benzamide (3)

To a stirring solution of 5-amino-2-chloropyridine (129 mg, 1 mmol) and 25 N,N-diisopropylethylamine (209 μL, 1.2 mmol) in dry acetonitrile (5 mL) was added 3-(trifluoromethyl)benzoyl chloride (151 μL, 1 mmol). The resulting solution was heated at 55°C for 3h. After cooling to room temperature ethyl acetate (10 mL) was

added and the solution was washed with water (2 x 10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude material was purified by column chromatography (4:1, hexane/ethyl acetate) to afford the desired product as a white solid (284 mg, 94%).

5

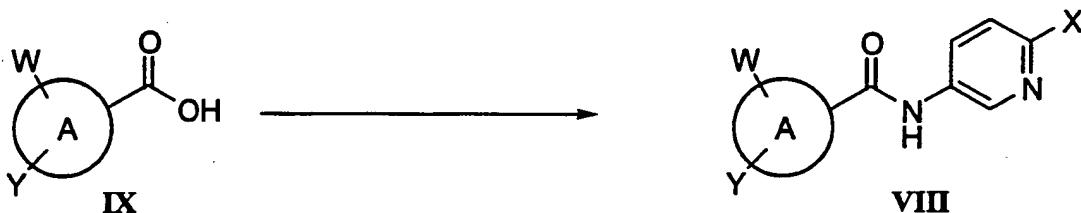
EXAMPLE 3

Preparation of Benzanilides from Acids

Benzanilides (VIII) may be also be prepared from acids (IX) by initially converting them to their acid chlorides (VII). Acids (IX) were treated with oxalyl chloride in the presence of catalytic N, N-dimethylformamide in an organic solvent such as dichloromethane or tetrahydrofuran preferably at 0 °C. The acid chloride, generated *in situ* was then reacted with aminopyridines (II, IV or VI) in the presence of a tertiary amine base such as triethylamine in an organic solvent such as dichloromethane or tetrahydrofuran. The reactions were typically performed at RT.

15

Scheme 6

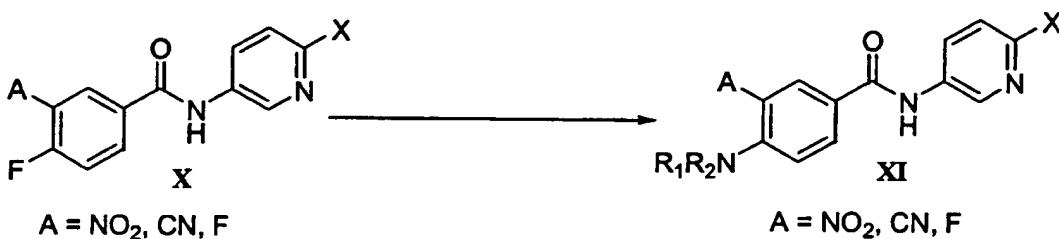


3.1 General experimental for Scheme 6

Oxalyl chloride (1.05 mmol) was added dropwise to a stirring suspension 20 of acid (IX) (1 mmol) and DMF (0.1 mmol) in dry DCM (5 mL) at 0 °C. Once addition was complete the reaction was allowed to warm to RT and stirred for a further 45 min whereupon the reaction was a clear solution. This solution was added dropwise to a stirring solution of aminopyridine (II or VI) (0.95 mmol) and N, N-diisopropylethylamine (2.2 mmol) in DCM (5 mL) at RT. After 30 min the organics were washed with aqueous 25 1N NaOH (10 mL), brine (10 mL) and dried (Na_2SO_4). The filtered solution was concentrated under reduced pressure and the crude product was purified by column chromatography (hexanes/ethyl acetate) or by crystallization (hexane/dichloromethane). Compounds prepared via this procedure include, compounds 16-24, 26, 28 and 37.

EXAMPLE 4**Preparation of 4-Amino Substituted Benzamides via Nucleophilic Displacement**

Aryl fluorides (X) (Scheme 7) possessing strongly electron withdrawing groups in either the ortho or para positions were displaced with primary or secondary 5 amines under elevated temperatures in a polar organic solvent such as DMSO or NMP to yield compounds of the formula (XI).

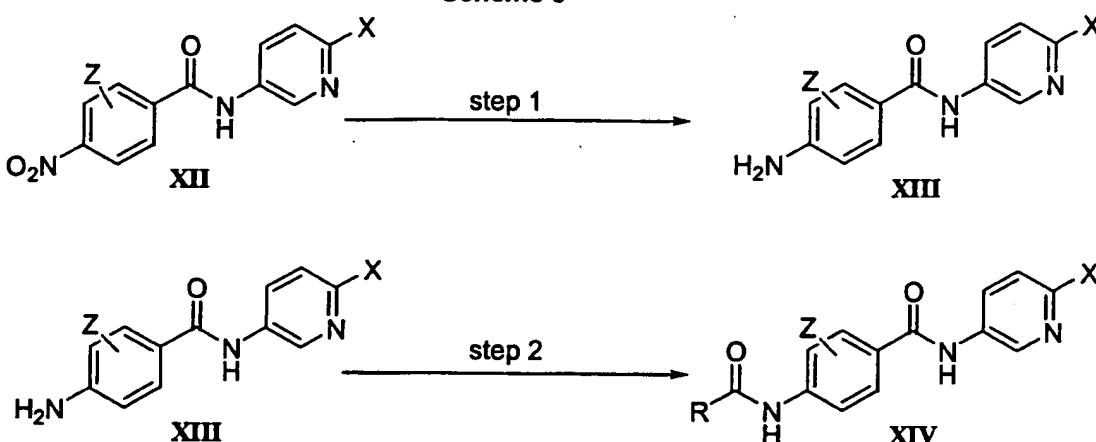
Scheme 7**10 4.1 General experimental for Scheme 7**

A solution of amine (1.1 mmol) and (X) (1 mmol) in either dry NMP or DMSO (3 mL) was heated at 120 °C for 12h. After cooling to RT, water (10 mL) and ethyl acetate (10 mL) were added. After vortexing for several minutes the organic layer was removed and dried (Na₂SO₄). The solvent was removed under reduced pressure and 15 the residue purified by column chromatography (hexanes/ethyl acetate or acetone/chloroform). The products (XI) were obtained as white solids (30-50%). Compounds prepared via this procedure include, compounds 30-34.

EXAMPLE 5**20 Reduction of Aromatic Nitro to Amine**

Scheme 8 outlines a general synthetic route to compounds of formulae (XIII) and (XIV).

Scheme 8



5.1 General experimental for Scheme 8

Compounds of structure (XII) were prepared using either general procedure B or C. Tin (II) chloride hydrate (22 mmol) was added to a stirring solution of (XII) in DMF (20 mL) at RT. After 14h, 6N NaOH (6 mL) was added and the suspension was stirred vigorously for 10 min. The organics were extracted with ethyl acetate (2 x 20 mL), washed with brine (2 x 10 mL) and dried (Na_2SO_4). The filtered solutions were concentrated under reduced pressure and the crude products were purified by column chromatography (hexanes/ethyl acetate; 1:2) to afford the desired intermediates (XIII) as a white solids (60-90%).

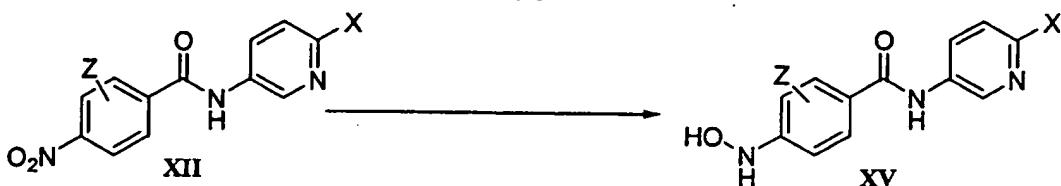
The intermediates (XIII) (0.2 mmol) were coupled with either acid chlorides (VI) or acids (0.2 mmol) using the methods described in general procedures A and B. The desired products (XIV) were obtained as tan solids (20-60%). Compounds prepared via this procedure include, compound 35.

EXAMPLE 6

Preparation of 4-Hydroxyamino Compounds (XV).

Hydroxyamines (XV) were prepared according to the synthetic route outlined in Scheme 9.

Scheme 9



6.1 General Experimental for Scheme 9

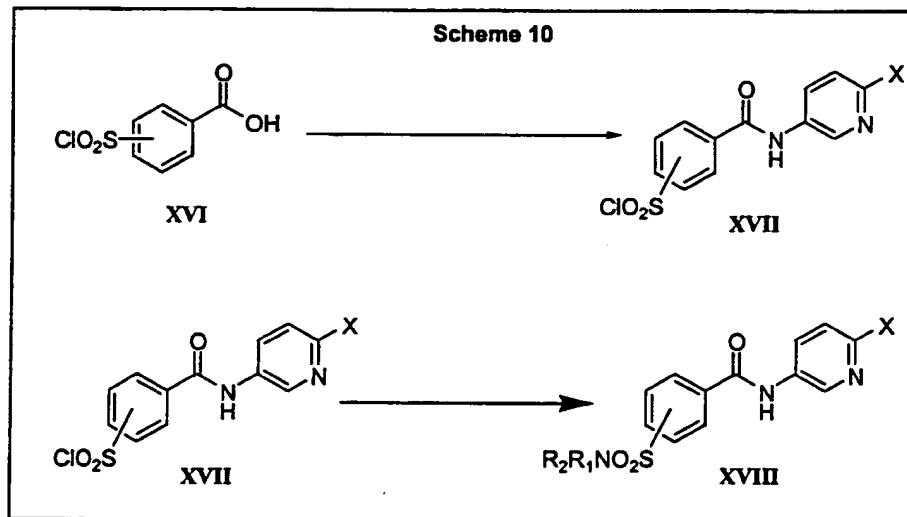
Tin (II) chloride hydrate (3 mmol) was added to a stirring solution of nitrobenzamide (XII) (1 mmol) in DMF (5 mL) at RT. After 3h, 6N NaOH (6 mL) was 5 added and the suspension was stirred vigorously for 10 min. The organics were extracted with ethyl acetate (2 x 20 mL), washed with brine (2 x 10 mL) and dried (Na_2SO_4). The filtered solution was then concentrated under reduced pressure to afford the crude product. Purification by column chromatography (ethyl acetate) gave the desired products (XV) as beige solids (50-70%).

10

EXAMPLE 7

Preparation of Sulfonamides

Sulfonamides (e.g., XVIII) were prepared using the chemistry outlined in Scheme 10. Intermediate (XVII) were generated by coupling an aminopyridine (II or IV) 15 with an activated form of (XVI). Subsequent coupling of the sulfonyl group with an amine generated the desired sulfonamides (XVIII)



20

7.1 General Experimental for Scheme 10

Oxalyl chloride (175 μL , 2 mmol) was added dropwise to a stirring solution of (XVI) (440 mg, 2 mmol) and DMF (20 μL , cat) in THF (8 mL) at 0 °C. After addition was complete the reaction was allowed to warm to RT. After 30 min the reaction was cooled back to 0 °C whereupon a solution of (II or IV) (1.9 mmol) and N, N-

diisopropylethylamine (700 μ L, 4 mmol) in THF (2.3 mL) was added. After stirring for 30 min at RT, this solution of (XVII) (0.18 M) was used directly without further manipulation.

A solution of (XVII) (5.5 mL, 1 mmol) in THF was added to a stirring 5 solution of amine (1 mmol) and N, N-diisopropylethylamine (3 mmol) in THF (2 mL) at RT. After 1h, water (10 mL) and ethyl acetate (10 mL) were added. The organic layer was separated, washed with water (5 mL), aqueous 1N NaOH (5 mL), aqueous 1N HCl (5 mL) and then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue purified by column chromatography (hexanes/ethyl acetate; 1:2). The products 10 were obtained as white solids (60-80%). Compounds prepared via this procedure include, compounds 36 and 40.

EXAMPLE 8

The compounds of the invention were characterized using a combination 15 of melting point, ^1H NMR and mass spectrometry. The results of the characterization are presented below. The structures for the compounds set forth below are provided in FIG. 1.

3,4-Dichloro-N-pyridin-3-yl-benzamide (1): mp 165-166 °C; ^1H NMR (300 MHz, DMSO-d₆) δ 10.58 (1H, brs), 8.87 (1H, d, J = 2.3 Hz), 8.30 (1H, dd, J= 4.7, 1.4 Hz), 8.19 (1H, d, J= 1.9Hz), 8.16-8.12 (1H, m), 7.91 (1H, dd, J= 8.4, 2.1Hz), 7.80 (1H, d, J= 8.5Hz) and 7.38 (1H, dd, J= 8.4, 4.7Hz); MS (ESI) *m/z*: 266.9 [M+H]⁺.

3,4-Dichloro-N-(6-chloro-pyridin-3-yl)-benzamide (2): mp 188-189 °C; ^1H NMR (300 MHz, CDCl₃) δ 7.36 (1H,d, J = 8.7 Hz), 7.58 (1H, d, J = 9.3 Hz), 7.70 (1H, dd, J= 9.4, 2.0 Hz), 7.90 (1H, brs), 7.96 (1H, d, J= 1.9 Hz), 8.24 (1H, dd, J= 8.7, 2.8 Hz) and 8.48 (1H, d, J=2.8 Hz); ^{13}C NMR (75 MHz, DMSO-d₆) δ 124.7, 128.6; 130.2, 131.4, 131.9, 134.8, 135.4, 142.0, 144.9 and 164.0; MS (ESI) *m/z*: 301.1 [M+H]⁺.

N-(6-Chloro-pyridin-3-yl)-3-trifluoromethyl-benzamide (3): mp 139-140 °C; ^1H NMR (300 MHz, CDCl₃) δ 7.35 (1H, d, J = 8.7 Hz), 7.63 (1H, t, J = 7.8 Hz), 7.82 (1H, d, J= 7.8 Hz), 8.06 (1H, d, J= 7.8 Hz), 8.11 (1H, brs), 8.25 (1H, dd, J = 8.7, 2.9 Hz), 8.36 (1H, s) and 8.50 (1H, d, J= 2.6 Hz); ^{19}F NMR (282 MHz, CDCl₃) δ -63.6; ^{13}C NMR (75 MHz,

DMSO-d₆) δ 124.2, 124.2, 124.6, 129.0, 129.7, 130.6, 130.9, 133.7, 134.6, 141.2 and 164.8; MS (ESI) *m/z*: 301.2 [M+H]⁺.

N-(6-Chloro-pyridin-3-yl)-3,4-difluoro-benzamide (4): mp; 164 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 7.51 (1H, d, J = 8.7 Hz), 7.59-7.68 (1H, m), 7.84-7.88 (1H, m), 8.03 (1H, ddd, J= 11.3, 7.9, 2.1 Hz), 8.19-8.23 (1H, m), 8.25 (1H, d, J= 2.0 Hz) and 10.64 (1H, s); ¹⁹F NMR (282 MHz, DMSO-d₆) δ -112.9 (m), -115.2 (m); ¹³C NMR (75 MHz, DMSO-d₆) δ 117.9 (dd, J= 18.3, 49.8 Hz), 124.7, 125.7 (dd, J= 3.4, 6.9 Hz), 131.5 (m), 131.9, 135.3, 142.1, 145.0, 149.3 (dd, J= 14.7, 201.0 Hz), 152.8 (dd, J= 12.6, 205.0 Hz), 164.6; MS (ESI) *m/z*: 269.1 [M+H]⁺.

3-Chloro-N-(6-chloro-pyridin-3-yl)-benzamide (5): mp 153-154 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.67 (1H, brs), 8.74 (1H, d, J = 2.6 Hz), 8.22 (1H, dd, J= 8.7, 2.8 Hz), 7.99 (1H, d, J= 1.7 Hz), 7.90 (1H, d, J= 7.8 Hz), 7.69 (1H, d, J= 7.1 Hz), 7.58 (1H, t, J= 7.8 Hz) and 7.51 (1H, d, J= 8.7 Hz); MS (ESI) *m/z*: 267.0 [M+H]⁺.

Biphenyl-4-carboxylic acid (6-chloro-pyridin-3-yl)-amide (6): mp 227-229 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.62 (1H, brs), 8.81 (1H, d, J = 2.3 Hz), 8.26 (1H, dd, J= 8.7, 2.4 Hz), 8.06 (2H, d, J= 8.2 Hz), 7.85 (2H, d, J= 8.2 Hz), 7.75 (2H, d, J= 7.5 Hz), 7.53-7.47 (3H, m) and 7.42 (1H, q, J= 7.1 Hz); MS (ESI) *m/z*: 309.2 [M+H]⁺.

6-Chloro-N-(6-chloro-pyridin-3-yl)-nicotinamide (7): mp 228 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.81 (1H, brs), 8.92 (1H, d, J = 2.3 Hz), 8.73 (1H, d, J= 2.6Hz), 8.32 (1H, dd, J= 8.4, 2.4 Hz), 8.19 (1H, dd, J= 8.7, 2.8 Hz), 7.71 (1H, d, J= 8.4 Hz) and 7.52 (1H, d, J= 8.7 Hz); MS (ESI) *m/z*: 268.1 [M+H]⁺.

3,4-Difluoro-N-(6-methyl-pyridin-3-yl)-benzamide (8): ¹H NMR (300 MHz, DMSO-d₆) δ 10.42 (1H, brs), 8.73 (1H, d, J = 2.3 Hz), 8.04-7.97 (2H, m), 7.86-7.82 (1H, m), 7.90 (1H, dt, J= 10.4, 8.4 Hz), 7.23 (1H, d, J= 8.5 Hz) and 2.42 (3H, s); ¹⁹F NMR (282 MHz, DMSO-d₆) δ -133.1 to -133.3 (1H, m) and -137.1 (1H, q, J= 10.7Hz); MS (ESI) *m/z*: 249.0 [M+H]⁺.

N-(6-Chloro-pyridin-3-yl)-3-fluoro-benzamide (9): mp 160 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.63 (1H, brs), 8.75 (1H, d, J = 2.8 Hz), 8.20 (1H, dd, J= 8.7, 2.8 Hz), 7.79 (1H, d, J= 7.8 Hz), 7.75 (1H, d, J= 11.1 Hz), 7.62-7.55 (1H, m) and 7.53-7.43 (2H, m); ¹⁹F NMR (282 MHz, DMSO-d₆) δ -112.0 (q, 8.5Hz); MS (ESI) *m/z*: 251.0 [M+H]⁺.

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N-(6-Chloro-pyridin-3-yl)-3-(trifluoromethyl)-benzamide (10): mp 169-170 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.81 (1H, brs), 8.75 (1H, d, J = 2.8 Hz), 8.22 (1H, dd, J= 8.7, 2.8 Hz), 8.13 (1H, d, J= 8.2 Hz), 7.91 (2H, d, J= 8.4 Hz) and 7.52 (2H, d, J= 8.7 Hz); ¹⁹F NMR (282 MHz, DMSO-d₆) δ -61.4 (s); MS (ESI) *m/z*: 301.2 [M+H]⁺.

10

N-(6-Chloro-pyridin-3-yl)-4-fluoro-3-trifluoromethyl-benzamide (11): mp 149-150 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.63 (1H, brs), 8.76 (1H, d, J = 2.6 Hz), 8.22 (1H, dd, J= 8.7, 2.8 Hz), 7.98 (2H, d, J= 8.7 Hz), 7.63 (1H, d, J= 8.7 Hz) and 7.52 (1H, d, J= 8.7 Hz); MS (ESI) *m/z*: 319.1 [M+H]⁺.

15

N-(6-Chloro-pyridin-3-yl)-3-fluoro-4-trifluoromethyl-benzamide (12): mp 182 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.78 (1H, brs), 8.75 (1H, d, J = 2.3 Hz), 8.37-8.32 (2H, m), 8.22 (1H, dd, J= 8.7, 2.6 Hz), 7.73 (1H, m) and 7.54 (1H, d, J= 8.7 Hz); ¹⁹F NMR (282 MHz, DMSO-d₆) δ -60.1 (3F, m), -110.7 (m); MS (ESI) *m/z*: 319.1 [M+H]⁺.

20

N-(6-Chloro-pyridin-3-yl)-4-fluoro-benzamide (13): mp 163-164 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.58 (1H, brs), 8.76 (1H, d, J = 2.6 Hz), 8.22 (1H, dd, J= 8.7, 2.6 Hz), 8.04 (1H, d, J= 8.7 Hz), 8.02 (1H, d, J= 8.7 Hz), 7.51 (1H, d, J= 8.7 Hz) and 7.39 (2H, t, J= 8.8 Hz); ¹⁹F NMR (282 MHz, DMSO-d₆) δ -107.7 (m); MS (ESI) *m/z*: 319.0 [M+H]⁺.

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N-(6-Chloro-pyridin-3-yl)-4-chloro-benzamide (14): mp 197-199 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.63 (1H, brs), 8.76 (1H, d, J = 2.6 Hz), 8.22 (1H, dd, J= 8.7, 2.8 Hz), 7.98 (2H, d, J= 8.7 Hz), 7.63 (1H, d, J= 8.7 Hz) and 7.52 (1H, d, J= 8.7 Hz); MS (ESI) *m/z*: 267.0 [M+H]⁺.

30

5,6-Difluoro-N-(6-fluoro-pyridin-3-yl)-nicotinamide (15): mp 135-137 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.58 (1H, brs), 8.52 (1H, s), 8.29-8.23 (1H, m), 8.03-7.97 (1H, m), 7.87-7.82 (1H, m), 7.65-7.56 (1H, m) and 7.19 (1H,dd, J= 8.9, 3.1 Hz); ¹⁹F NMR (282

MHz, DMSO-d₆) δ -73.6 (1F, d, J= 6.5Hz), -132.9 (1H, q, J= 10.7Hz) and -137.1 (1H, q, J= 10.7Hz); MS (ESI) m/z: 253.0 [M+H]⁺.

N-(6-Chloro-pyridin-3-yl)-3-methyl-4-nitro-benzamide (16): mp 192-193 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.81 (1H, brs), 8.74 (1H, d, J = 2.6 Hz), 8.21 (1H, dd, J= 8.7, 2.8 Hz), 8.09 (1H, d, J= 8.4 Hz), 8.02 (1H, s), 7.94 (1H, dd, J= 8.5, 1.6 Hz), 7.52 (1H, d, J= 8.7Hz) and 2.58 (3H, s); MS (ESI) m/z: 292.2 [M+H]⁺.

5-Fluoro-1H-indole-2-carboxylic acid (6-chloro-pyridin-3-yl)-amide (17): mp 290 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 11.92 (1H, brs), 10.58 (1H,brs), 8.79 (1H, s), 8.25 (1H, dd, J= 8.7 and 2.4 Hz), 7.53-7.41 (4H, m) and 7.10 (1H, t, J= 7.1 Hz); ¹⁹F NMR (282 MHz, DMSO-d₆) δ -123.0 (m); MS (ESI) m/z: 290.0 [M+H]⁺.

5-Chloro-1H-indole-2-carboxylic acid (6-chloro-pyridin-3-yl)-amide (18): mp 296 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 12.03 (1H, brs), 10.62 (1H, brs), 8.80 (1H, d, J= 2.6 Hz), 8.24 (1H, dd, J= 8.7 and 2.6 Hz), 7.79 (1H, s) 7.52 (1H, d, J= 8.7 Hz), 7.42 (1H, d, J= 8.9 Hz), 7.41 (1H, s) and 7.23 (1H, dd, J= 8.7, 1.9 Hz); MS (ESI) m/z: 306.0 [M+H]⁺.

5-Chloro-benzofuran-2-carboxylic acid (6-chloro-pyridin-3-yl)-amide (19): mp 222-223 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 11.00 (1H, brs), 8.78 (1H, d, J = 2.6 Hz), 8.24 (1H, dd, J= 8.7, 2.8 Hz), 7.90 (1H, d, J= 2.1 Hz), 7.76 (1H, s,), 7.73 (1H, d, J= 8.9 Hz) and 7.51 (2H, d, J= 8.9 Hz); MS (ESI) m/z: 306.9 [M+H]⁺.

5-Chloro-thiophene-2-carboxylic acid (6-chloro-pyridin-3-yl)-amide (20): mp 215-216 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.61 (1H, brs), 8.68 (1H, d, J = 2.8 Hz), 8.14 (1H, dd, J= 8.7, 2.6 Hz), 7.88 (1H, d, J= 4.2 Hz), 7.50 (1H, d, J= 8.5 Hz) and 7.27 (1H, d, J= 4.0 Hz); ¹³C NMR (75 MHz, DMSO-d₆) δ 159.7, 144.8, 142.0, 138.5, 135.3, 135.2, 131.5, 130.4, 129.0 and 124.7.0; MS (ESI) m/z: 273.0 [M+H]⁺.

5-Chloro-furan-2-carboxylic acid (6-chloro-pyridin-3-yl)-amide (21): mp 143-144 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.59 (1H, brs), 8.72 (1H, d, J = 2.4 Hz), 8.18 (1H, dd, J= 8.7, 2.6 Hz), 7.50 (1H, d, J= 8.7 Hz), 7.43 (1H, d, J= 3.5 Hz) and 6.76 (1H, d, J= 3.7 Hz); MS (ESI) m/z: 257.1 [M+H]⁺.

4,5-Dichloro-isothiazole-3-carboxylic acid (6-chloro-pyridin-3-yl)-amide (22): mp 199-201 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 11.16 (1H, brs), 8.75 (1H, d, J = 2.6 Hz), 8.20 (1H, dd, J= 8.7, 2.8 Hz) and 7.51 (1H, d, J= 8.7 Hz); MS (ESI) *m/z*: 307.9[M+H]⁺.

5

3-Methyl-1H-indole-2-carboxylic acid (6-chloro-pyridin-3-yl)-amide (23): mp 184-185 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.64 (1H, brs), 8.75 (1H, d, J = 2.6 Hz), 8.21 (1H, dd, J= 8.7, 2.8 Hz), 7.68 (1H, d, J= 8.0 Hz), 7.54 (1H, d, J= 8.5 Hz), 7.50 (2H, d, J= 8.9 Hz), 7.34 (1H, s), 7.31 (1H, t, J= 7.1 Hz), 7.13 (1H, t, J= 7.1 Hz) and 3.98 (3H, s); MS (ESI) *m/z*: 286.1 [M+H]⁺.

10

5-Ethyl-1H-indole-2-carboxylic acid (6-chloro-pyridin-3-yl)-amide (24): mp 270 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 11.67 (1H, brs), 10.49 (1H, brs), 8.80 (1H, s), 8.25 (1H, dd, J= 8.7 and 2.8 Hz), 7.51 (1H, d, J= 8.7 Hz), 7.46 (1H, s), 7.36 (1H, d, J= 8.7 Hz), 7.35 (1H, s), 7.10 (1H, d, J= 8.5 Hz), 2.66 (2H, q, J= 7.7 Hz) and 1.21 (1H, t, J= 7.7 Hz); ¹³C NMR (75 MHz, DMSO-d₆) δ 160.6, 144.3, 141.7, 136.2, 136.0, 131.1, 127.6, 125.6, 124.7, 120.4, 112.8, 104.8, 28.8 and 16.8; MS (ESI) *m/z*: 300.2 [M+H]⁺.

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N-(6-Chloro-pyridin-3-yl)-benzamide (25): mp 163-164 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.59 (1H, brs), 8.74 (1H, d, J = 2.6 Hz), 8.21 (1H, dd, J= 8.7, 2.8 Hz), 7.94 (1H, s), 7.92 (1H, d, J= 1.6 Hz), 7.59 (1H, d, J= 7.1 Hz) and 7.55-7.49 (3H, m); MS (ESI) *m/z*: 233.0 [M+H]⁺.

20

1H-Indole-2-carboxylic acid (6-chloro-pyridin-3-yl)-amide (26): mp 260-263 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 11.85 (1H, brs), 10.62 (1H, brs), 8.78 (1H, d, J = 2.6 Hz), 8.23 (1H, dd, J= 8.7, 2.8 Hz), 7.66 (1H, d, J= 8.0 Hz), 7.51 (1H, d, J= 8.5 Hz), 7.45 (1H, d, J= 8.4 Hz), 7.41-7.40 (1H, m), 7.23 (1H, t, J= 7.1 Hz) and 7.06 (1H, d, J= 7.3 Hz); MS (ESI) *m/z*: 272.0 [M+H]⁺.

25

Benzof[b]thiophene-2-carboxylic acid (6-chloro-pyridin-3-yl)-amide (27): mp 226-227 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.86 (1H, brs), 8.75 (1H, d, J = 2.6 Hz), 8.34 (1H, s), 8.21 (1H, dd, J= 8.7, 2.8 Hz), 8.06-7.99 (2H, m) and 7.54-7.48 (3H, m); MS (ESI) *m/z*: 289.1 [M+H]⁺.

5-Fluoro-1H-indole-2-carboxylic acid (6-methyl-pyridin-3-yl)-amide (28): mp 303-304 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 11.88 (1H, brs), 10.36 (1H, brs), 9.05 (1H, d, J = 1.9 Hz), 8.06 (1H, dt, J = 8.4, 2.1 Hz), 7.45 (2H, m), 7.39 (1H, s), 7.24 (1H, d, J = 8.3 Hz), 5 7.08 (1H, dt, J = 9.2, 2.4 Hz) and 2.43 (3H, s); ¹⁹F NMR (282 MHz, DMSO-d₆) δ -123.2; MS (ESI) *m/z*: 270.2 [M+H]⁺.

3,4-Difluoro-N-(6-trifluoromethyl-pyridin-3-yl)-benzamide (29): mp 175-176 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.84 (1H, brs), 9.05 (1H, d, J = 1.8 Hz), 8.45 (1H, dd, J = 10 8.5, 1.9 Hz), 8.07 (1H, ddd, J = 9.9, 7.6, 2.1 Hz), 7.93 (1H, d, J = 8.5 Hz) and 7.89-7.86 (1H, m); ¹⁹F NMR (282 MHz, DMSO-d₆) δ -65.7 (3F, s), -132.5 (1F, m) and -137.0 (1F, m); MS (ESI) *m/z*: 303.1 [M+H]⁺.

N-(6-Chloro-pyridin-3-yl)-3-fluoro-4-pyrrolidin-1-yl-benzamide (30): mp 215-216 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.23 (1H, brs), 8.71 (1H, d, J = 2.6 Hz), 8.18 (1H, dd, J = 8.7, 2.4 Hz), 7.70 (1H, s), 7.65 (1H, d, J = 3.1 Hz), 7.46 (1H, d, J = 8.9 Hz), 6.73 (1H, t, J = 8.5 Hz), 3.42-3.40 (4H, m) and 1.91-1.88 (4H, m); ¹⁹F NMR (282 MHz, DMSO-d₆) δ -129.0 (s); MS (ESI) *m/z*: 320.2 [M+H]⁺.

20 N-(6-Chloro-pyridin-3-yl)-3-fluoro-4-morpholin-4-yl-benzamide (31): mp 228-229 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.41 (1H, s), 8.75 (1H, d, J = 2.6 Hz), 8.20 (1H, dd, J = 8.7 and 2.6 Hz), 7.79 (1H, s), 7.74 (1H, d, J = 7.7 Hz), 7.50 (1H, d, J = 8.7 Hz), 7.13 (1H, t, J = 9.2 Hz), 3.74 (4H, m) and 3.12 (4H, m); ¹³C NMR (75 MHz, DMSO-d₆) δ 164.8, 155.7, 152.5, 144.4, 143.3 (d, J = 7 Hz), 142.0, 135.9, 131.4, 127.3 (d, J = 7 Hz), 125.5, 25 124.6, 118.7 (d, J = 3 Hz), 66.5 and 50.4 (d, J = 5 Hz); MS (ESI) *m/z*: 336.2 [M+H]⁺.

N-(6-Chloro-pyridin-3-yl)-3-fluoro-4-imidazol-1-yl-benzamide (32): mp 215-218 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.71 (1H, s), 8.78 (1H, s), 8.24 (1H, dt, J = 8.7, 1.6 Hz), 8.17 (1H, s), 8.07 (1H, dd, J = 12.0, 1.6 Hz), 7.96 (1H, dd, J = 8.4, 1.7 Hz), 7.88 (1H, t, J = 8.2 Hz), 7.69 (1H, s), 7.53 (1H, d, J = 8.7 Hz) and 7.17 (1H, s); ¹⁹F NMR (282 MHz, DMSO-d₆) δ -123.1 (t, J = 8.8 Hz); MS (ESI) *m/z*: 317.1 [M+H]⁺.

N-(6-Chloro-pyridin-3-yl)-3-fluoro-4-[(pyridin-2-ylmethyl)-amino]-benzamide (33): mp 210-211 °C; ^1H NMR (300 MHz, DMSO-d₆) δ 10.20 (1H, brs), 8.69 (1H, d, J = 2.6 Hz), 8.50 (1H, d, J = 4.7 Hz), 8.15 (1H, dd, J = 8.7, 2.8 Hz), 7.75-7.64 (2H, m), 7.45 (1H, d, J = 8.7 Hz), 7.31 (1H, d, J = 8.0 Hz), 7.25 (1H, dd, J = 6.4, 5.1 Hz), 6.63 (1H, t, J = 8.7 Hz) and 5 4.49 (2H, d, J = 5.9 Hz); ^{19}F NMR (282 MHz, DMSO-d₆) δ -134.3 (m); MS (ESI) *m/z*: 357.0 [M+H]⁺.

N-(6-Chloro-pyridin-3-yl)-4-dimethylamino-3-fluoro-benzamide (34): mp 170-171 °C; ^1H NMR (300 MHz, DMSO-d₆) δ 10.32 (1H, brs), 8.76 (1H, s), 8.21 (1H, d, J = 8.7 Hz), 10 7.75 (1H, s), 7.71 (1H, d, J = 5.8 Hz), 7.59 (1H, d, J = 8.7 Hz), 7.02 (1H, t, J = 9.2 Hz) and 2.92 (6H, s); ^{19}F NMR (282 MHz, DMSO-d₆) δ -122.6 (t, J = 10.7 Hz); MS (ESI) *m/z*: 294.2 [M+H]⁺.

Pyridine-2-carboxylic acid [4-(6-chloro-pyridin-3-ylcarbamoyl)-phenyl]-amide (35): mp 15 258-260 °C; ^1H NMR (300 MHz, DMSO-d₆) δ 10.92 (1H, s), 10.50 (1H, s), 8.78 (1H, d, J = 2.6 Hz), 8.75 (1H, d, J = 4.7 Hz), 8.24 (1H, dd, J = 8.7 and 2.6 Hz), 8.17 (1H, d, J = 7.8 Hz), 8.09 (2H, d, J = 7.8 Hz), 8.08 (1H, m), 7.98 (2H, d, J = 8.7 Hz), 7.70 (1H, dd, J = 6.4, 5.0 Hz) and 7.50 (1H, d, J = 8.7 Hz); ^{13}C NMR (75 MHz, DMSO-d₆) δ 165.8, 163.5, 150.0, 149.0, 144.4, 142.3, 141.9, 138.8, 136.1, 131.4, 129.4, 129.2, 127.7, 124.6, 123.1 20 and 120.1; MS (ESI) *m/z*: 353.2 [M+H]⁺.

N-(6-Chloro-pyridin-3-yl)-4-(morpholine-4-sulfonyl)-benzamide (36): ^1H NMR (300 MHz, DMSO-d₆) δ 10.88 (1H, s), 8.78 (1H, d, J = 2.6 Hz), 8.24 (1H, dd, J = 8.7 and 2.6 Hz), 8.19 (2H, d, J = 8.5 Hz), 7.90 (2H, d, J = 8.5 Hz), 7.50 (1H, d, J = 8.7 Hz), 3.62 (4H, m) and 2.90 (4H, m); ^{13}C NMR (75 MHz, DMSO-d₆) δ 165.3, 144.9, 142.1, 138.8, 25 137.9, 135.7, 131.5, 129.4, 128.3, 124.7, 65.8 and 46.8; MS (ESI) *m/z*: 382.1 [M+H]⁺.

N-(6-Chloro-pyridin-3-yl)-3-fluoro-4-nitro-benzamide (37): mp 205 °C; ^1H NMR (300 MHz, DMSO-d₆) δ 10.87 (1H, brs), 8.69 (1H, d, J = 2.4 Hz), 8.32 (1H, t, J = 7.8 Hz), 8.22 30 (1H, dd, J = 8.7, 2.6 Hz), 8.10 (1H, dd, J = 11.8, 1.6 Hz), 7.96 (1H, d, J = 8.5 Hz) and 7.53 (1H, d, J = 8.7 Hz); MS (ESI) *m/z*: 294.0 [M-H]⁺.

N-(6-Chloro-pyridin-3-yl)-4-hydroxyamino-benzamide (38): dec 200 °C; ^1H NMR (300 MHz, DMSO-d₆) δ 10.24 (1H, brs), 8.86 (1H, s), 8.75 (1H, d, J = 2.4 Hz), 8.61 (1H, s), 8.22 (1H, dd, J = 8.7, 2.8 Hz), 7.83 (2H, d, J = 8.5 Hz) and 7.47 (1H, d, J = 8.7 Hz); MS (ESI) *m/z*: 261.9 [M-H]⁺.

5

N-(6-Chloro-pyridin-3-yl)-3-fluoro-4-hydroxyamino-benzamide (39): ^1H NMR (300 MHz, DMSO-d₆) δ 10.16 (1H, brs), 8.74 (1H, d, J = 2.6 Hz), 8.19 (1H, dt, J = 8.7, 2.8 Hz), 7.66 (1H, dd, J = 12.7, 1.7 Hz), 7.60 (1H, d, J = 8.4 Hz), 7.47 (1H, d, J = 8.7 Hz), 6.80 (1H, t, J = 8.9 Hz) and 5.93 (2H, brs); MS (ESI) *m/z*: 280.0 [M-H]⁺.

10

N-(6-Chloro-pyridin-3-yl)-4-methylsulfamoyl-benzamide (40): mp 186-189 °C; ^1H NMR (300 MHz, DMSO-d₆) δ 10.78 (1H, brs), 8.77 (1H, d, J = 2.3 Hz), 8.23 (1H, dt, J = 8.7, 2.8 Hz), 8.13 (2H, d, J = 8.4 Hz), 7.99 (1H, d, J = 8.2 Hz), 7.63 (1H, q, J = 5.2 Hz), 7.53 (1H, d, J = 8.7 Hz) and 2.43 (3H, s); MS (ESI) *m/z*: 326.2 [M+H]⁺.

15

4-Amino-N-(6-chloro-pyridin-3-yl)-3-fluoro-benzamide (41): mp 193 °C; ^1H NMR (300 MHz, DMSO-d₆) δ 10.16 (1H, brs), 8.73 (1H, d, J = 2.6 Hz), 8.20 (1H, dd, J = 8.7, 2.8 Hz), 7.66 (1H, dd, J = 12.7, 1.7 Hz), 7.59 (1H, dd, J = 8.4, 1.9 Hz), 7.46 (1H, d, J = 8.7 Hz), 6.80 (1H, t, J = 8.7 Hz) and 5.94 (2H, s); MS (ESI) *m/z*: 266.0 [M+H]⁺.

20

N-(6-Chloro-pyridin-3-yl)-4-nitro-benzamide (42): mp 193 °C; ^1H NMR (300 MHz, DMSO-d₆) δ 10.88 (1H, brs), 8.77 (1H, d, J = 2.3 Hz), 8.39 (1H, s), 8.36 (1H, s), 8.23 (1H, dt, J = 8.7, 2.8 Hz), 8.20 (1H, s), 8.17 (1H, s), 7.63 (1H, q, J = 5.2 Hz) and 7.54 (1H, d, J = 8.7 Hz); MS (ESI) *m/z*: 275.9 [M+H]⁺.

25

N-(6-Chloro-pyridin-3-yl)-3-chloro-4-fluoro-benzamide (43): mp 173 °C; ^1H NMR (300 MHz, DMSO-d₆) δ 10.65 (1H, brs), 8.74 (1H, s), 8.23-8.18 (2H, m), 8.01-7.97 (1H, m), 7.61 (1H, t, J = 9.1 Hz) and 7.52 (1H, d, J = 8.7 Hz); MS (ESI) *m/z*: 285.0 [M+H]⁺.

30

EXAMPLE 9

This example illustrates a KCNQ2 screening protocol for evaluating compounds of the present invention.

Cells expressing voltage-gated K⁺ channels, such as KCNQ2-like channels were loaded with ⁸⁶Rb⁺ by culture in media containing ⁸⁶RbCl. Following loading, culture media was removed and the cells were washed in EBSS to remove residual traces of ⁸⁶Rb⁺. Cells were preincubated with drug (0.01 – 30 μM in EBSS) and 5 then ⁸⁶Rb⁺ efflux was stimulated by exposing cells to EBSS solution supplemented with a sub-maximal concentration of KCl (generally 7-20 mM) in the continued presence of drug. After a suitable efflux period, the EBSS/ KCl solution was removed from the cells and the ⁸⁶Rb⁺ content determined by Cherenkov counting (Wallac Trilux). Cells were then lysed with a SDS solution and the ⁸⁶Rb⁺ content of the lysate determined. Percent 10 ⁸⁶Rb⁺ efflux was calculated according to:

$$(\text{⁸⁶Rb}^+ \text{ content in EBSS}/(\text{⁸⁶Rb}^+ \text{ content in EBSS} + \text{⁸⁶Rb}^+ \text{ content of the lysate})) * 100$$

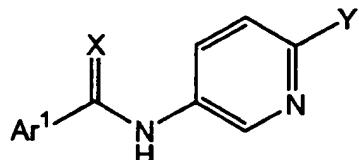
Efflux was normalized to the maximal ⁸⁶Rb⁺ efflux (*i.e.*, that induced by 15 a high concentration of KCl, generally 30-135 mM).

Compounds 1-43 (FIG.1) were prepared according to the general methods set forth in the examples and they were assayed using the above-described method. The activity of the assayed compounds ranged from about 30% to greater than about 70% efflux.

20 It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety 25 for all purposes.

WHAT IS CLAIMED IS:

1 1. A compound having the formula:



2 wherein,

3 Ar¹ is a member selected from the group consisting of aryl, substituted
4 aryl, heteroaryl and substituted heteroaryl;

5 X is a member selected from the group consisting of O, S and N-R¹,
6 wherein, R¹ is a member selected from the group consisting of H,
7 (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, heteroalkyl, substituted
8 heteroalkyl, aryl, substituted aryl, heteroaryl, substituted
9 heteroaryl, aryl(C₁-C₄)alkyl, substituted aryl(C₁-C₄)alkyl, CN,
10 -C(O)R², -OR³, -C(O)NR³R⁴, and -S(O)₂NR³R⁴;
11 wherein, R² is a member selected from the group consisting of
12 (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, cycloalkyl,
13 substituted cycloalkyl, heteroalkyl, substituted heteroalkyl,
14 heterocyclyl, substituted heterocyclyl, alkaryl, substituted
15 aryl, heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl and
16 substituted aryl(C₁-C₄)alkyl;

17 R³ and R⁴ are each members independently selected from the group
18 consisting of hydrogen, (C₁-C₈)alkyl, substituted
19 (C₁-C₈)alkyl, cycloalkyl, substituted cycloalkyl,
20 heteroalkyl, substituted heteroalkyl, heterocyclyl,
21 substituted heterocyclyl, aryl, substituted aryl, heteroaryl,
22 substituted heteroaryl, aryl(C₁-C₄)alkyl and substituted
23 aryl(C₁-C₄)alkyl, or R³ and R⁴ can be combined with the
24 nitrogen to which each is attached to form a 5-, 6- or
25 7-membered ring optionally having additional heteroatoms
26 at the ring vertices; and

27 Y is a member selected from the group consisting of halogen, C₁-C₄ alkyl,
28 C₁-C₄ substituted alkyl, -OCH₃ and -OCF₃.

1 2. The compound according to claim 1, wherein Ar¹ is a member
2 selected from the group consisting of phenyl, substituted phenyl, indolyl, substituted
3 indolyl, benzofuranyl, substituted benzofuranyl, furanyl, substituted furanyl, thienyl,
4 substituted thienyl, isothiazolyl, substituted isothiazolyl, pyrazolyl and substituted
5 pyrazolyl.

1 3. The compound according to claim 2, wherein Ar¹ is a member
2 selected from the group consisting of substituted phenyl, substituted or unsubstituted 2-
3 indolyl and substituted or unsubstituted 2-thienyl.

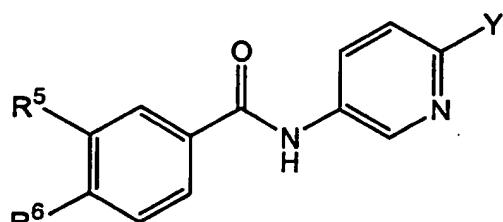
1 4. The compound according to claim 3, wherein X is O.

5. The compound according to claim 3, wherein the Ar¹ substituents
are selected from the group consisting of halogen, alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy,
halo(C₁-C₄)alkoxy, nitro, cyano, -NR⁷C(O)R⁸, -NR⁷R⁸, phenyl and substituted phenyl,
wherein

5 R⁷ and R⁸ are members independently selected from hydrogen,
6 (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, cycloalkyl, substituted
7 cycloalkyl, heteroalkyl, substituted heteroalkyl, heterocyclyl,
8 substituted heterocyclyl, aryl, substituted aryl, heteroaryl,
9 substituted heteroaryl, aryl(C₁-C₄)alkyl and substituted
10 aryl(C₁-C₄)alkyl, or R⁷ and R⁸ taken together with the nitrogen to
11 which each is attached form a 5-, 6- or 7-membered ring optionally
12 having additional heteroatoms at the ring vertices.

1 6. The compound according to claim 2, wherein Ar¹ is substituted
2 phenyl.

1 7. The compound according to claim 6, having the formula:

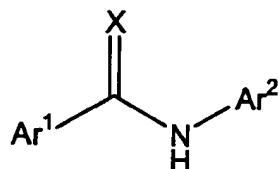


3 such as:

4 R⁵ and R⁶ are members independently selected from the group consisting
 5 of H, halogen, substituted or unsubstituted alkyl, halo(C₁-C₄)alkyl, nitro, cyano and
 6 substituted or unsubstituted phenyl, with the proviso that both R⁵ and R⁶ are not H.

1 8. The compound according to claim 7, wherein R⁵ and R⁶ are
 2 members independently selected from the group consisting of H, F, and Cl, with the
 3 proviso that both R⁵ and R⁶ are not H.

1 9. A method of increasing ion flow through voltage-dependent
 2 potassium channels in a cell, said method comprising contacting said cell with a
 3 potassium channel-opening amount of a compound of the formula:



4 wherein

5 6 Ar¹ and Ar² are each members independently selected from the group
 7 consisting of aryl, substituted aryl, heteroaryl and substituted
 8 heteroaryl; and

9 9 X is a member selected from the group consisting of O, S and N-R¹,
 10 wherein R¹ is a member selected from the group consisting of H,
 11 (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, aryl, substituted aryl,
 12 heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl, substituted
 13 aryl(C₁-C₄)alkyl, CN, -C(O)R², -OR³, -C(O)NR³R⁴, and
 14 -S(O)₂NR³R⁴;

15 wherein R² is a member selected from the group consisting of
 16 (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, aryl, substituted aryl,
 17 heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl and
 18 substituted aryl(C₁-C₄)alkyl; and

19 R³ and R⁴ are each members independently selected from the group
 20 consisting of hydrogen, (C₁-C₈)alkyl, substituted
 21 (C₁-C₈)alkyl, aryl, substituted aryl, heteroaryl, substituted
 22 heteroaryl, aryl(C₁-C₄)alkyl and substituted
 23 aryl(C₁-C₄)alkyl, or R³ and R⁴ can be combined with the
 24 nitrogen to which each is attached to form a 5-, 6- or

25 7-membered ring optionally having additional heteroatoms
26 at the ring vertices.

1 **10.** The method according to claim 9, wherein said voltage-dependent
2 potassium channel is responsible for the M-current.

1 11. The method according to claim 9, wherein said voltage-dependent
2 potassium channel comprises KCNQ subunits.

1 12. The method according to claim 9, wherein Ar¹ is a member
2 selected from the group consisting of phenyl, substituted phenyl, indolyl, substituted
3 indolyl, benzofuranyl, substituted benzofuranyl, furanyl, substituted furanyl, thienyl,
4 substituted thienyl, isothiazolyl, substituted isothiazolyl, pyrazolyl and substituted
5 pyrazolyl.

1 **13.** The method according to claim 9, wherein Ar¹ is substituted
2 phenyl, substituted or unsubstituted 2-indolyl and substituted or unsubstituted 2-thienyl

14. The method according to claim 9, wherein X is O.

1 15. The method according to claim 13, wherein the Ar¹ substituents are
2 selected from the group consisting of halogen, alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy,
3 halo(C₁-C₄)alkoxy, nitro, cyano, -NHC(O)R⁷, -NHR⁷, phenyl and substituted phenyl,
4 wherein

R⁷ is a member selected from hydrogen, (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, cycloalkyl, substituted cycloalkyl, heteroalkyl, substituted heteroalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl and substituted aryl(C₁-C₄)alkyl, or R⁷ can be combined with the nitrogen to which it is attached to form a 5-, 6- or 7-membered ring optionally having additional heteroatoms at the ring vertices.

1 **16.** The method according to claim 9, wherein Ar² is selected from the
2 group consisting of heteroaryl and substituted heteroaryl.

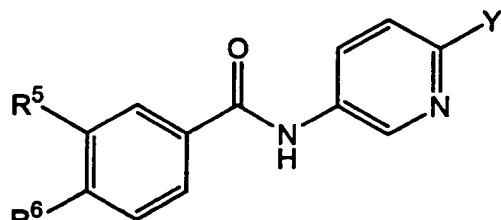
1 17. The method according to claim 9, wherein Ar¹ is substituted aryl;
2 Ar² is heteroaryl or substituted heteroaryl; and X is O.

1 **18.** The method according to claim 15, wherein Ar² is pyridyl or
2 substituted pyridyl.

1 **19.** The method according to claim 18, wherein Ar² is selected from
2 the group consisting of 6-methyl-3-pyridyl and 2-chloro-5-pyridyl.

1 **20.** The method according to claim 18, wherein Ar¹ is substituted
2 phenyl.

1 **21.** The method according to claim 20, said compound having the
2 formula:

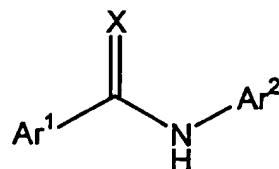


3 wherein,

5 R⁵ and R⁶ are members independently selected from the group consisting
6 of H, halogen, alkyl, halo(C₁-C₄)alkyl, nitro, cyano and phenyl, with the proviso that both
7 R⁵ and R⁶ are not H.

1 **22.** The method according to claim 21, wherein R⁵ and R⁶ are members
2 independently selected from the group consisting of H, F, and Cl, with the proviso that
3 both R⁵ and R⁶ are not H.

1 **23.** A method of treating a central or peripheral nervous system
2 disorder or condition through modulation of a voltage-dependent potassium channel, said
3 method comprising administering to a subject in need of such treatment, an effective
4 amount of a compound having the formula:



5 wherein

7 Ar¹ and Ar² are each members independently selected from the group
8 consisting of aryl, substituted aryl, heteroaryl and substituted
9 heteroaryl; and
10 X is a member selected from the group consisting of O, S and N-R¹,
11 wherein R¹ is a member selected from the group consisting of H,
12 (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, aryl, substituted aryl,
13 heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl, substituted
14 aryl(C₁-C₄)alkyl, CN, -C(O)R², -OR³, -C(O)NR³R⁴, and
15 -S(O)₂NR³R⁴;
16 wherein R² is a member selected from the group consisting of
17 (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, aryl, substituted aryl,
18 heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl and
19 substituted aryl(C₁-C₄)alkyl; and
20 R³ and R⁴ are each members independently selected from the group
21 consisting of hydrogen, (C₁-C₈)alkyl, substituted
22 (C₁-C₈)alkyl, aryl, substituted aryl, heteroaryl, substituted
23 heteroaryl, aryl(C₁-C₄)alkyl and substituted
24 aryl(C₁-C₄)alkyl, or R³ and R⁴ can be combined with the
25 nitrogen to which each is attached to form a 5-, 6- or
26 7-membered ring optionally having additional heteroatoms
27 at the ring vertices.

1 **24.** The method according to claim 23, wherein said disorder or
2 condition is selected from the group consisting of migraine, ataxia, Parkinson's disease,
3 bipolar disorders, spasticity, mood disorders, brain tumors, psychotic disorders,
4 myokymia, seizures, epilepsy, hearing loss, vision loss, Alzheimer's disease, age-related
5 memory loss, learning deficiencies, motor neuron diseases, and stroke.

1 **25.** The method according to claim 24, wherein said disorder or
2 condition is hearing loss.

1 **26.** The method according to claim 24, wherein said disorder or
2 condition is epilepsy or seizures.

1 **27.** The method according to claim 23, wherein Ar¹ is a member
2 selected from the group consisting of phenyl, substituted phenyl, indolyl, substituted
3 indolyl, benzofuranyl, substituted benzofuranyl, furanyl, substituted furanyl, thienyl,
4 substituted thienyl, isothiazolyl, substituted isothiazolyl, pyrazolyl and substituted
5 pyrazolyl.

1 **28.** The method according to claim 27, wherein Ar¹ is substituted aryl,
2 substituted or unsubstituted 2-indolyl and substituted or unsubstituted 2-thienyl.

1 **29.** The method according to claim 28, wherein X is O.

1 **30.** The method according to claim 28, wherein the Ar¹ substituents are
2 selected from the group consisting of halogen, alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy,
3 halo(C₁-C₄)alkoxy, nitro, cyano, -NHC(O)R⁷, -NHR⁷, phenyl and substituted phenyl,
4 wherein

5 R⁷ is a member selected from hydrogen, (C₁-C₈)alkyl, substituted
6 (C₁-C₈)alkyl, cycloalkyl, substituted cycloalkyl, heteroalkyl, substituted heteroalkyl,
7 heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted
8 heteroaryl, aryl(C₁-C₄)alkyl and substituted aryl(C₁-C₄)alkyl, or R⁷ can be combined with
9 the nitrogen to which it is attached to form a 5-, 6- or 7-membered ring optionally having
10 additional heteroatoms at the ring vertices.

1 **31.** The method according to claim 23, wherein Ar² is selected from
2 the group consisting of heteroaryl and substituted heteroaryl.

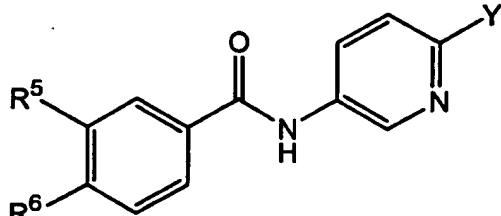
1 **32.** The method according to claim 23, wherein Ar¹ is substituted aryl;
2 Ar² is heteroaryl or substituted heteroaryl; and X is O.

1 **33.** The method according to claim 31, wherein Ar² is pyridyl or
2 substituted pyridyl.

1 **34.** The method according to claim 33, wherein Ar² is selected from
2 the group consisting of 6-methyl-3-pyridyl and 2-chloro-5-pyridyl.

1 **35.** The method according to claim 34, wherein Ar¹ is substituted
2 phenyl.

1 **36.** The method according to claim 35, said compound having the
2 formula:

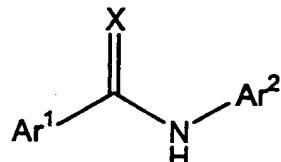


3 wherein,

4 **R⁵** and **R⁶** are members independently selected from the group consisting
5 of H, halogen, alkyl, halo(C₁-C₄)alkyl, nitro, cyano and phenyl, with the proviso that both
6 **R⁵** and **R⁶** are not H.
7

1 **37.** The method according to claim 36, wherein **R⁵** and **R⁶** are members
2 independently selected from the group consisting of H, F, and Cl, with the proviso that
3 both **R⁵** and **R⁶** are not H.

1 **38.** A composition comprising a pharmaceutically acceptable excipient
2 and a compound of the formula:



3 wherein,

4 **Ar¹** and **Ar²** are each members independently selected from the group
5 consisting of aryl, substituted aryl, heteroaryl and substituted
6 heteroaryl; and
7

8 **X** is a member selected from the group consisting of O, S and N-R¹,
9 wherein R¹ is a member selected from the group consisting of H,
10 (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, aryl, substituted aryl,
11 heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl, substituted
12 aryl(C₁-C₄)alkyl, CN, -C(O)R², -OR³, -C(O)NR³R⁴, and
13 -S(O)₂NR³R⁴;

14 wherein R² is a member selected from the group consisting of
15 (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, aryl, substituted aryl,

39. The composition according to claim 38, wherein Ar¹ is substituted aryl, substituted or unsubstituted 2-indolyl and substituted or unsubstituted 2-thienyl.

1 40. The composition according to claim 38, wherein X is O.

1 41. The composition according to claim 40, wherein the Ar¹
2 substituents are selected from the group consisting of halogen, alkyl, halo(C₁-C₄)alkyl,
3 (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, nitro, cyano, -NHC(O)R⁷, -NHR⁷, phenyl and
4 substituted phenyl, wherein
5 R⁷ is a member selected from hydrogen, (C₁-C₈)alkyl, substituted
6 (C₁-C₈)alkyl, cycloalkyl, substituted cycloalkyl, heteroalkyl, substituted heteroalkyl,
7 heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted
8 heteroaryl, aryl(C₁-C₄)alkyl and substituted aryl(C₁-C₄)alkyl, or R⁷ can be combined with
9 the nitrogen to which it is attached to form a 5-, 6- or 7-membered ring optionally having
10 additional heteroatoms at the ring vertices.

42. The composition according to 38, wherein Ar² is selected from the group consisting of heteroaryl and substituted heteroaryl.

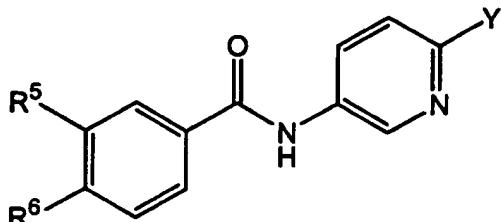
43. The composition according to claim 38, wherein Ar¹ is substituted aryl; Ar² is heteroaryl or substituted heteroaryl; and X is O.

44. The composition according to claim 42, wherein Ar² is pyridyl or substituted pyridyl.

1 **45.** The composition according to claim 44, wherein Ar² is selected
2 from the group consisting of 6-methyl-3-pyridyl and 2-chloro-5-pyridyl.

1 **46.** The composition according to claim 44, wherein Ar¹ is substituted
2 phenyl.

1 **47.** The composition according to claim 46, said compound having the
2 formula:



3
4 wherein,

5 R⁵ and R⁶ are members independently selected from the group consisting
6 of H, halogen, alkyl, halo(C₁-C₄)alkyl, nitro, cyano and phenyl, with the proviso that both
7 R⁵ and R⁶ are not H.

1 **48.** The composition according to claim 47, wherein R⁵ and R⁶ are
2 members independently selected from the group consisting of H, F, and Cl, with the
3 proviso that both R⁵ and R⁶ are not H.

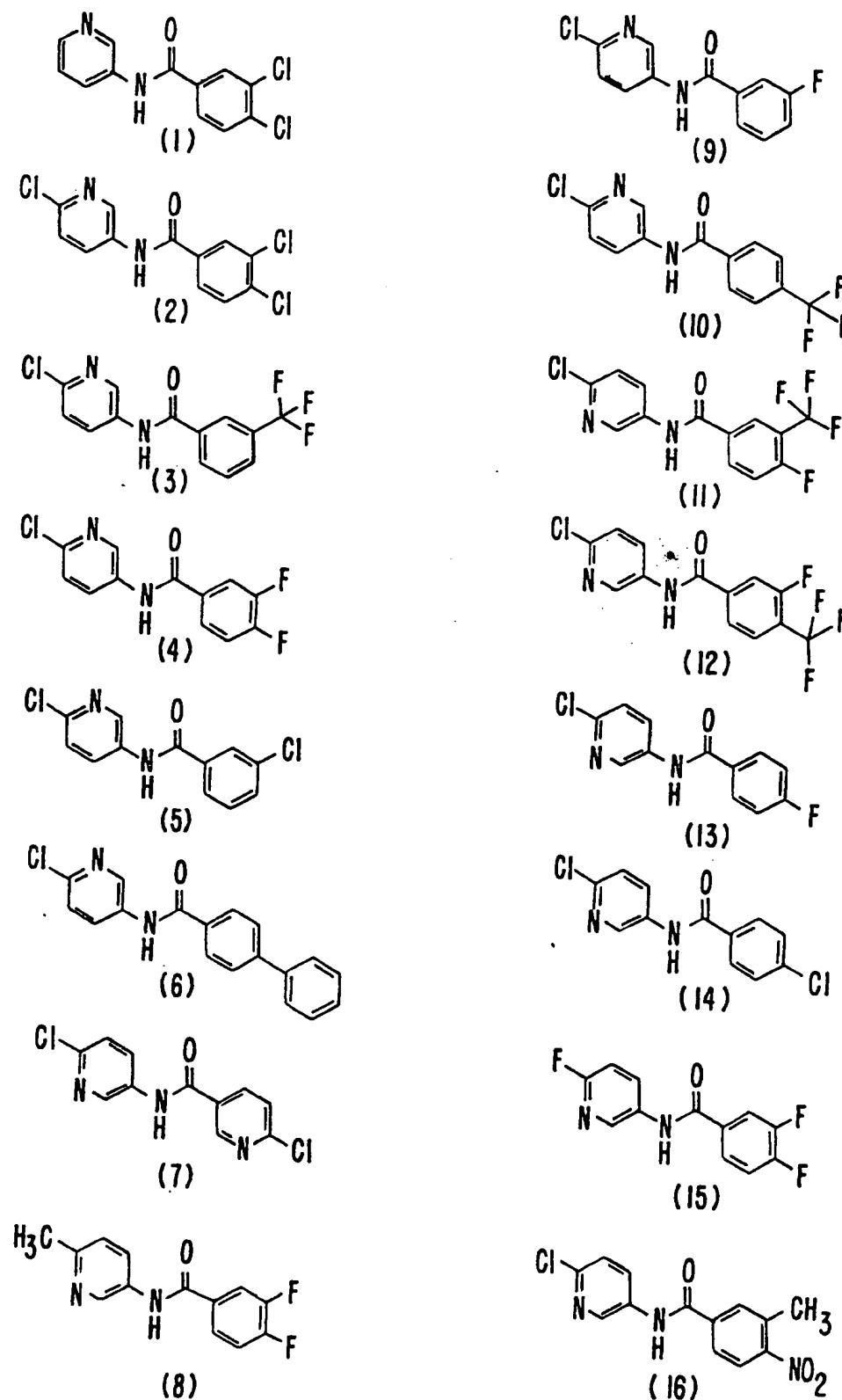
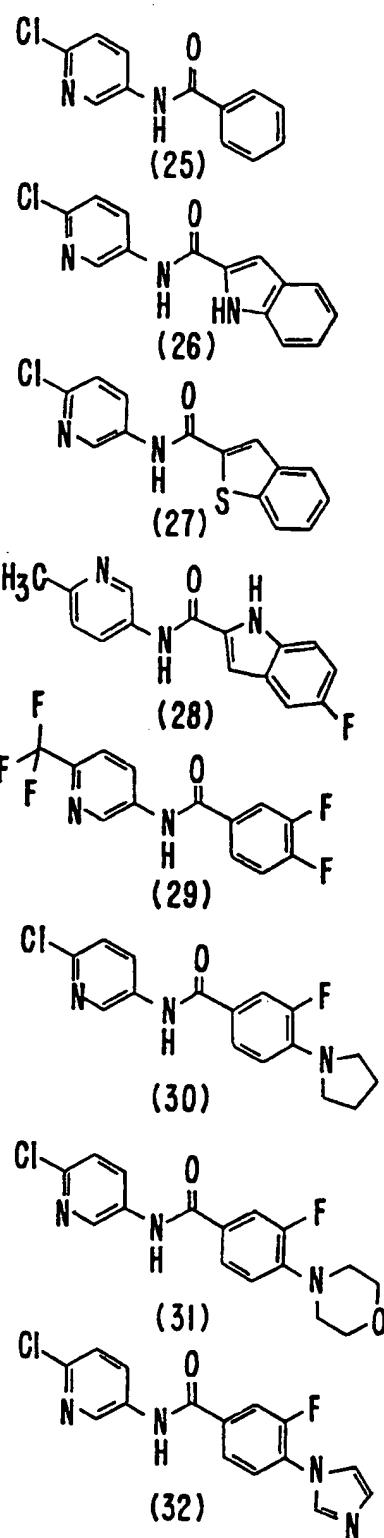
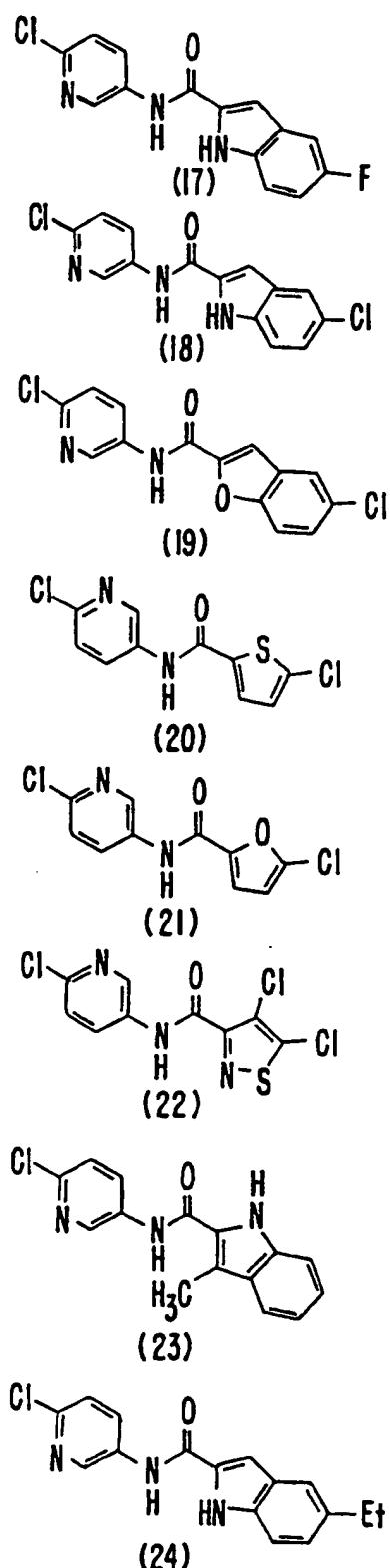
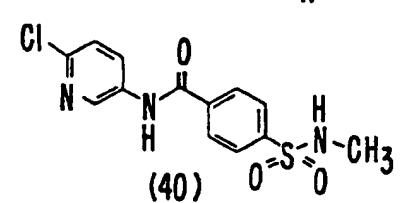
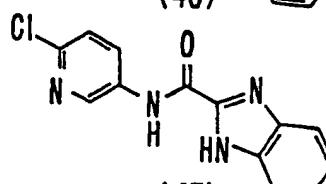
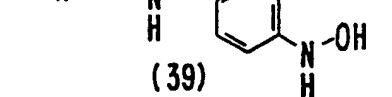
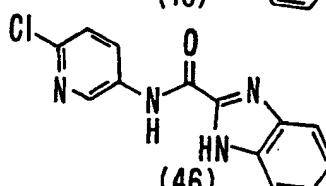
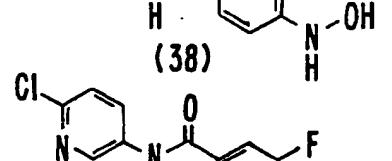
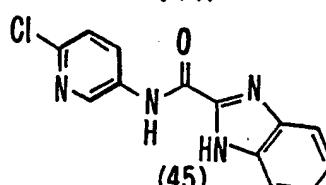
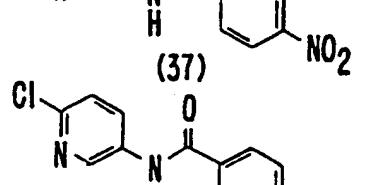
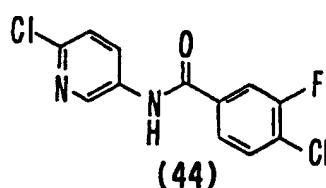
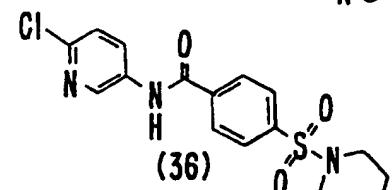
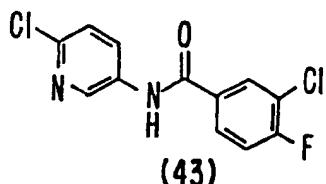
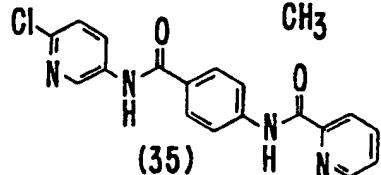
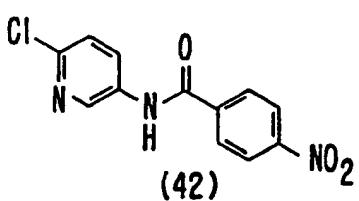
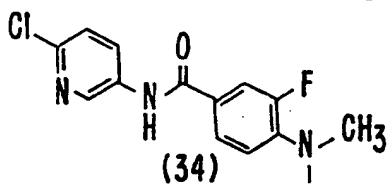
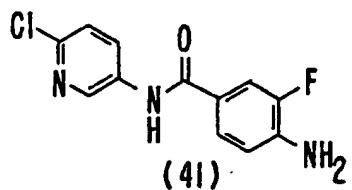
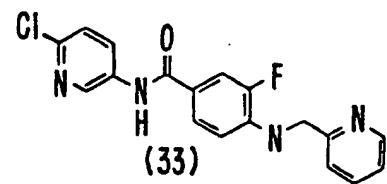
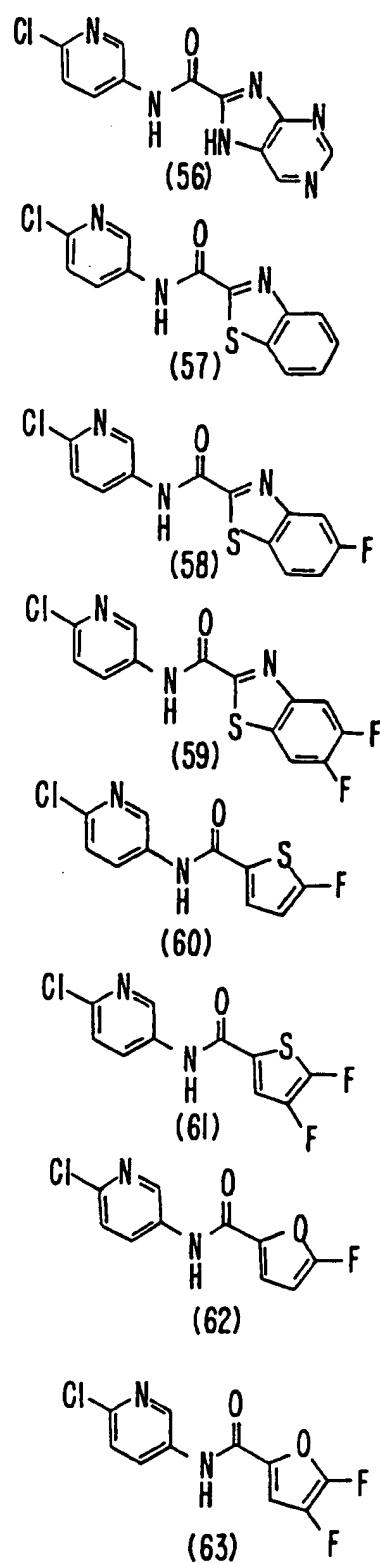
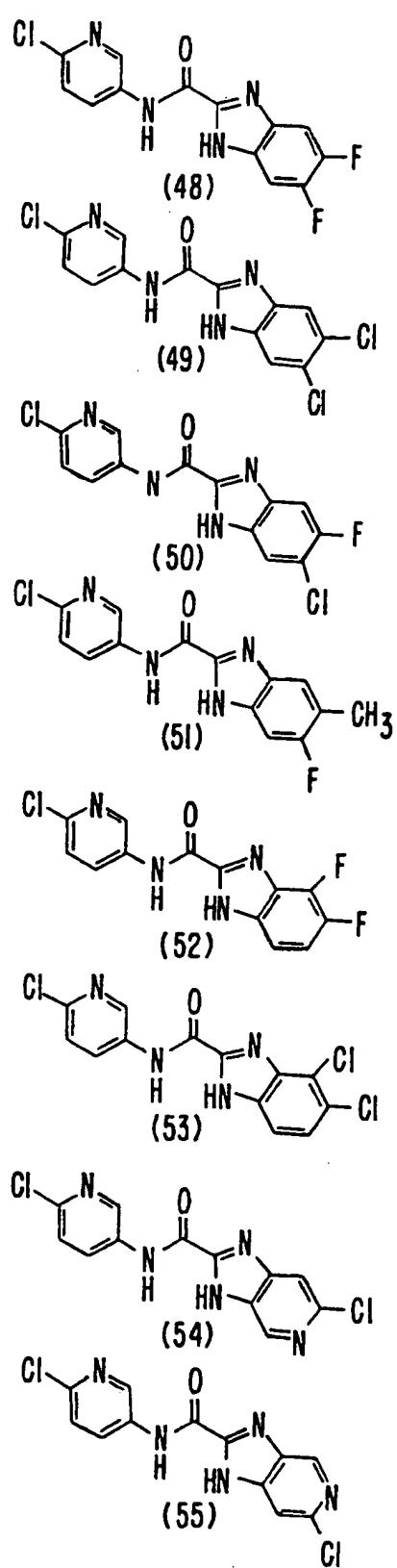


FIG. 1.

**FIG. 1. (CONT'D.)**

*FIG. 1. (CONT'D)*

*FIG. 1. (CONT'D)*

5/6

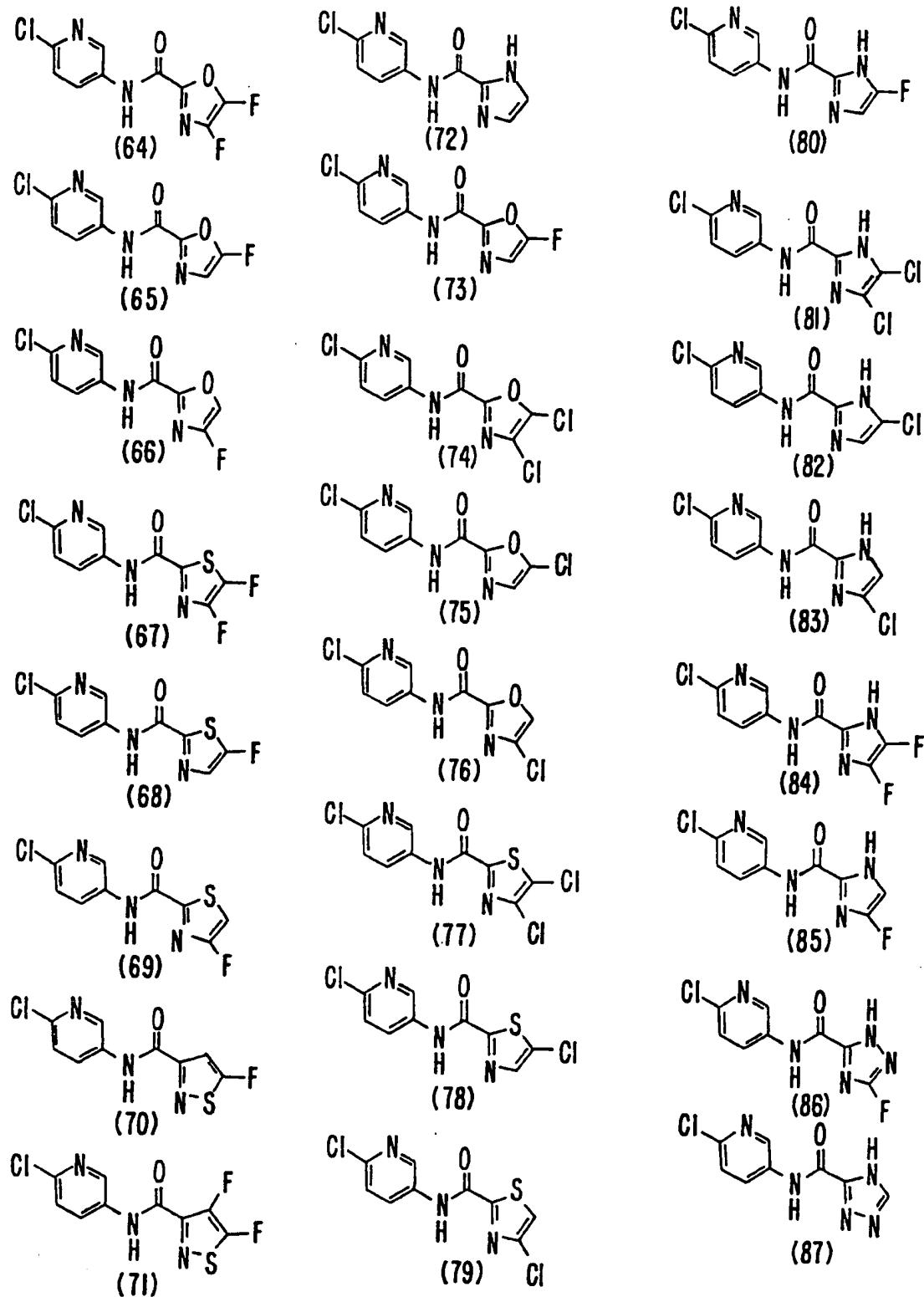
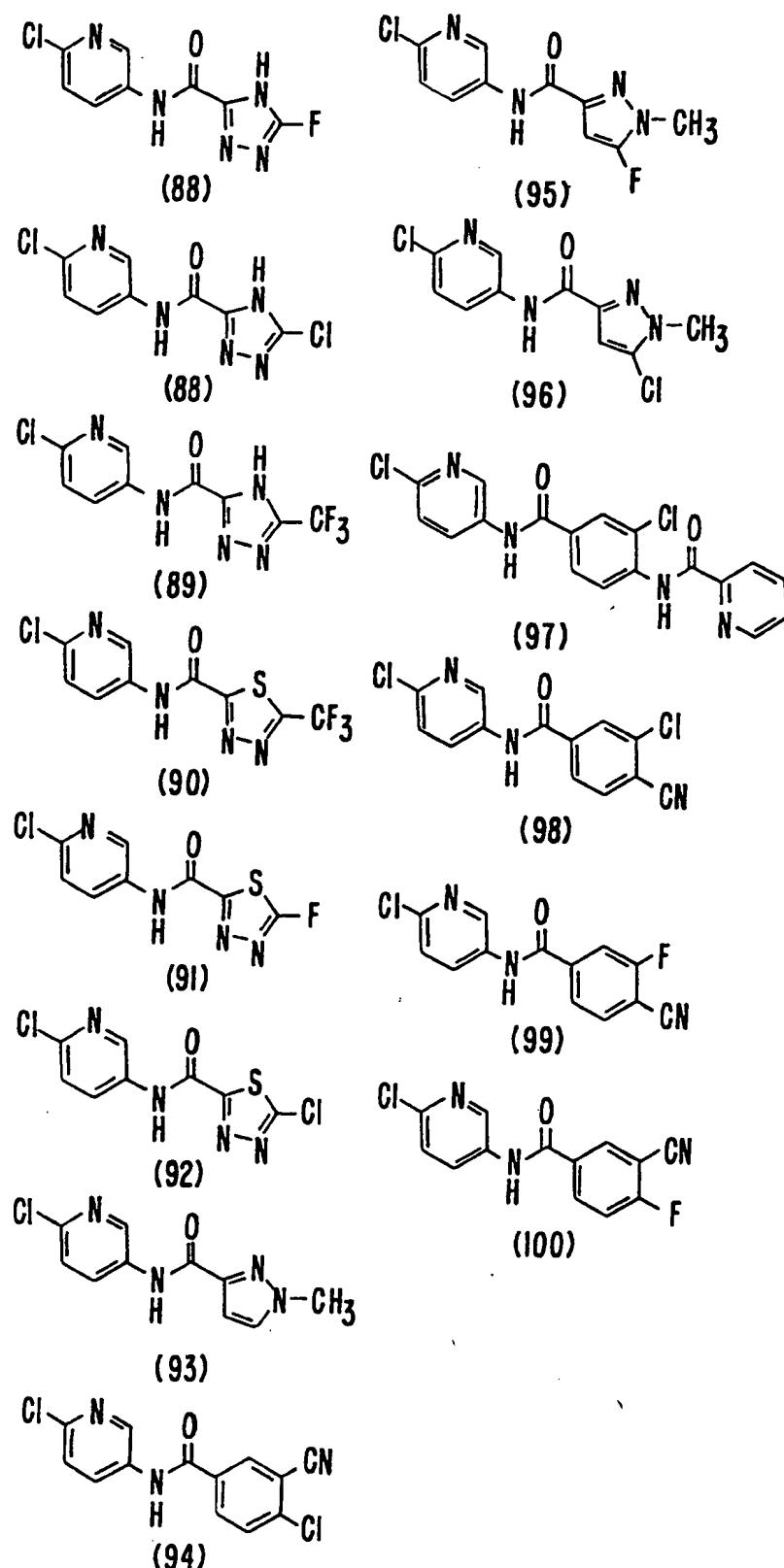


FIG. 1. (CONT'D)

**FIG. 1. (CONT'D.)**

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number
WO 01/10380 A3

(51) International Patent Classification⁷: **C07D 213/02**, 401/12, A61K 31/34, 31/38, 31/40, 31/41, 31/42, 31/44, 31/415, 31/425

(21) International Application Number: PCT/US00/21308

(22) International Filing Date: 4 August 2000 (04.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/147,221 4 August 1999 (04.08.1999) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

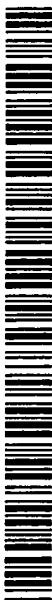
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
16 August 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/10380 A3

(54) Title: BENZANILIDES AS POTASSIUM CHANNEL OPENERS

(57) Abstract: Benzanilides are provided which are voltage-dependent potassium channel openers. Methods of using the benzanilides of the invention are also provided.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/21308

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CAS COMPUTER SEARCH 1966- TO DATE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,466,698 A (GLASE et al) 14 November 1995 (14.11.95), column 19, lines 15 and 16.	1-4 and 38-43
Y		1-4 and 38-43
X	SAWANISHI et al, Chemical Pharmaceutical Journal. Volume 35. No 8., August 1987, pages 3175-3182, especially page 3178.	1, 2 and 6
X	DE 3804346 A1 (BOEHRINGER MANNHEIM) 24 August 1989 (24.08.89), pages 8 and 10.	1-8, 38-44, and 46-48
Y		1-8, 38-44, and 46-48

Further documents are listed in the continuation of Box C.

See patent family annex.

• Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
• "A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
• "B" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
• "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
• "O" document referring to an oral disclosure, use, exhibition or other means		
• "P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

03 NOVEMBER 2000

Date of mailing of the international search report

08 FEB 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/21308

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---	DE 3305569 A1 (BAYER AG) 23 August 1984 (23.08.84), Example 31.	1-4, 6, 38-40, and 42-46 -----
Y		1-4, 6, 38-40, and 42-46 -----
X ---	DE 2343787 A1 (STERLING DRUG CO) 21 March 1974 (21.03.74), page 12, Example 1.	1, 38, 42 -----
Y		1, 38, 42 -----
X ---	EP 882,726 A1 (ELI LILLY AND COMPANY) 09 December 1998 (09.12.98), page 19, Examples 6 and 7.	1 ---
Y		1 -----
X ---	JP 57-131719 A2 (CHUGAI PHARMACEUTICAL) 14 August 1982 (14.08.82), Table 1, compound 8.	1, 38, 40, 42 and 44 -----
Y		1, 38, 40, 42 and 44 -----
X ---	JP 59-175467 A2 (CHUGAI PHARMACEUTICAL) 04 October 1984 (04.10.84), Table 1, compound 10.	1-8, 38-41 and 43-46 -----
Y		1-8, 38-41 and 43-46 -----
A	ARAKIDA et al., European Journal of Pharmacology. Volume 362, 1998, pages 229-233	1-48

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/21308

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/21308

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

C07D 213/02, 401/12;
A61K 31/34, 31/38, 31/40, 31/ 41, 31/42, 31/44, 31/415, 31/425

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

544/124,256; 546,118, 265, 268.7, 270.1, 271.1, 271.4, 272.4, 272.7, 273.1, 275.4, 277.4, 280.4, 281.1, 283.4,
284.1, 309
514/235.8, 258, 303, 332, 336, 337, 338, 339, 340, 341, 342, 349

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

546/118, 265, 268.7, 270.1, 271.1, 271.4, 272.4, 272.7, 273.1, 275.4, 277.4, 280.4, 281.1, 283.4, 309
514/235.8, 258, 303, 332, 336, 337, 338, 339, 340, 341, 342, 349

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-8, 9(in part), 10-22, 23(in part), 24-37, 38(in part), and 39-48, drawn to a chemical compound, composition and method of use wherein the formula of the compound is recited in claim 1 and Ar¹ is aryl.

Group II, claims 1-5, 9(in part), 10-20, 23(in part), 24-34, 38(in part), and 39-42, drawn to a chemical compound, composition and method of use wherein the formula of the compound is recited in claim 1 and Ar¹ is heteroaryl.

Group III, claims 9(in part), 10-15, 23(in part), 24-30, 38(in part), and 39-41, drawn to composition and method of use wherein Ar¹ and Ar² are aryl.

Group IV, claims 9(in part), 10-19, 23(in part), 24-31, 33, 34, 38(in part), 39-42, 44, and 45, drawn to composition and method of use wherein Ar¹ and Ar² are heteroaryl.

Group V, claims 9(in part), 10-19, 23(in part), 24-31, 33, 34, 38(in part), 39-42, 44, and 45, drawn to composition and method of use wherein Ar¹ is heteroaryl and Ar² is aryl.

Group VI, claims 1-8, 9(in part), 10-22, 23(in part), 24-37, 38(in part), and 39-48, drawn to a chemical compound, composition and method of use wherein Ar¹ is aryl and Ar² are heteroaryl other than the Group I invention.

The inventions listed as Groups I-VI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

There is a lack of a significant common structural feature in the Groups as recited above to which the claimed utility may be attributed. The common core in the group is a carbamoyl

functional group -C-N. The ring systems defined by Ar¹ and Ar² can be aryl and heteroaryl. There are various permutations for the claimed compounds, composition and method of use. Additionally, the ring systems in the Groups may include phenyl and pyridinyl, respectively. The various ring systems are not related as a recognized class of compounds.

Accordingly, the requirement of the unity of invention has been set forth because there exists no common core between the claims to include a single general inventive concept in which the utility can be attributed.